VOL. 32 NOVEMBER 1956 NO. 11

# BULLETIN

## OF THE NEW YORK ACADEMY OF MEDICINE

*Original Articles by*

HERBERT J. STACK

JOHN O. MOORE

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1. Am. Heart J. 42:260 (Aug.) 1950.
2. Ann. Int. Med. 40:520 (Apr.) 1954.
3. Am. J. M. Sc. 227:103 (Feb.) 1954
4. Ann. Int. Med. 39:1189 (Dec.) 1953.
5. Am. Heart J. 49:106 (Jan.) 1955.
6. Am. Heart J. 49:279 (Aug.) 1955.
7. Arch. Int. Med. 90:221 (Aug.) 1952.
8. Circulation 5:201 (Feb.) 1952.
9. New Eng. J. Med. 248:225 (Feb.) 1953.
10. Am. Heart J. 42:292 (Feb.) 1951.
11. Fed. Proc. 9:256 (Mar.) 1950.


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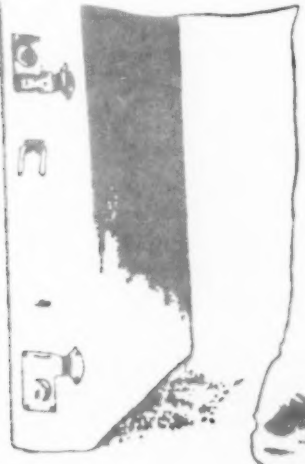

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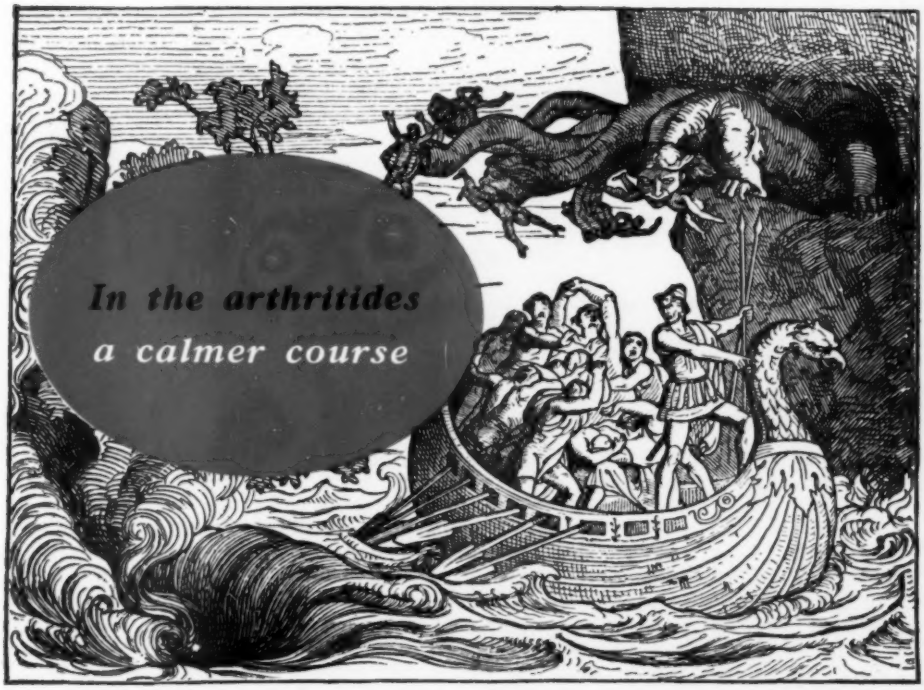


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[1] *Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med. 11:1105*

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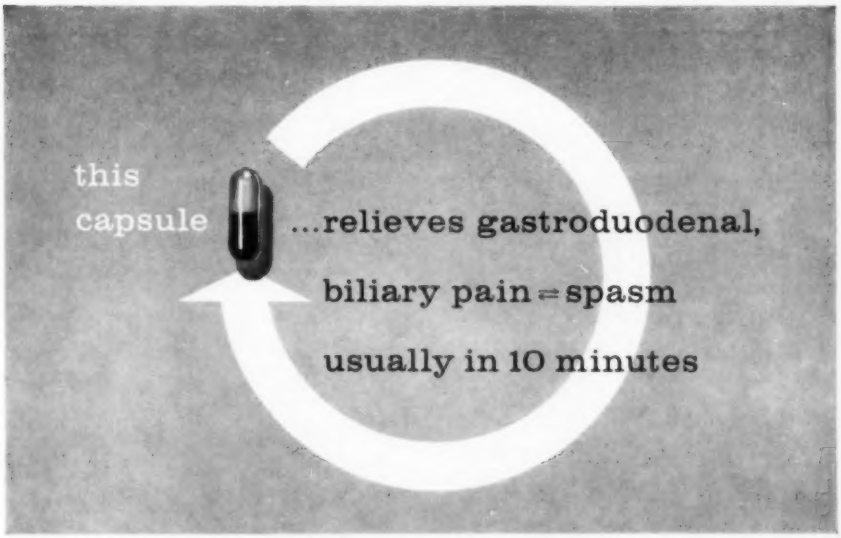


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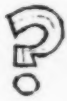
*measurements* *the whole world over.* Do you own a Baumanometer?  If not,

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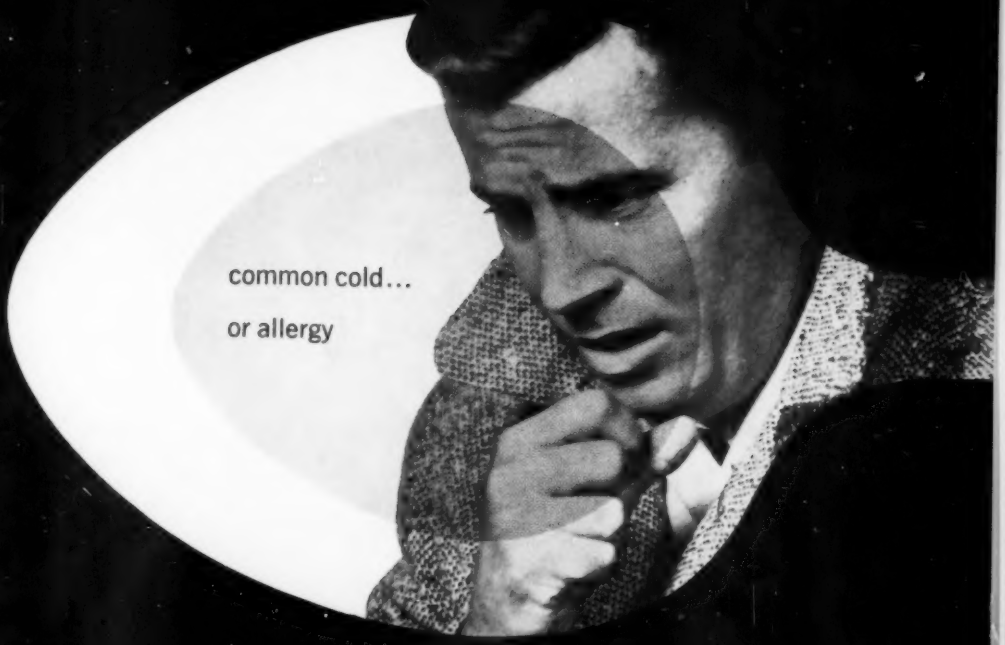


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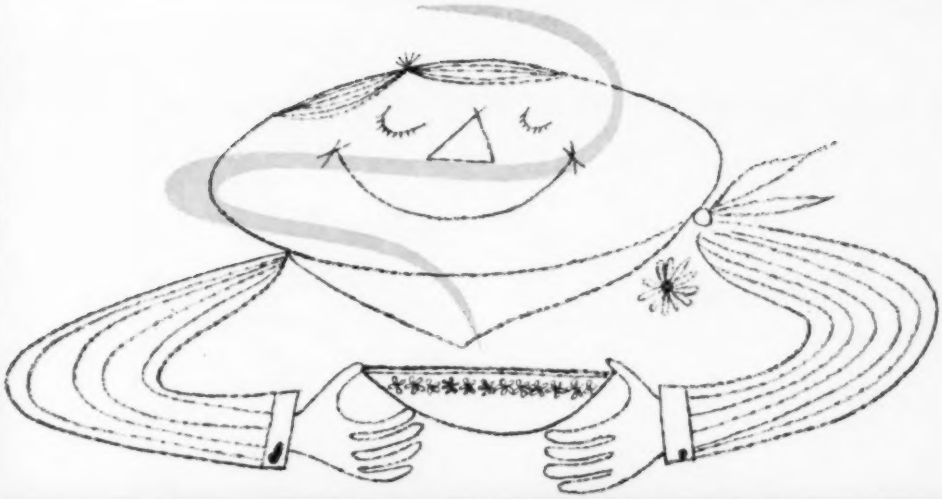

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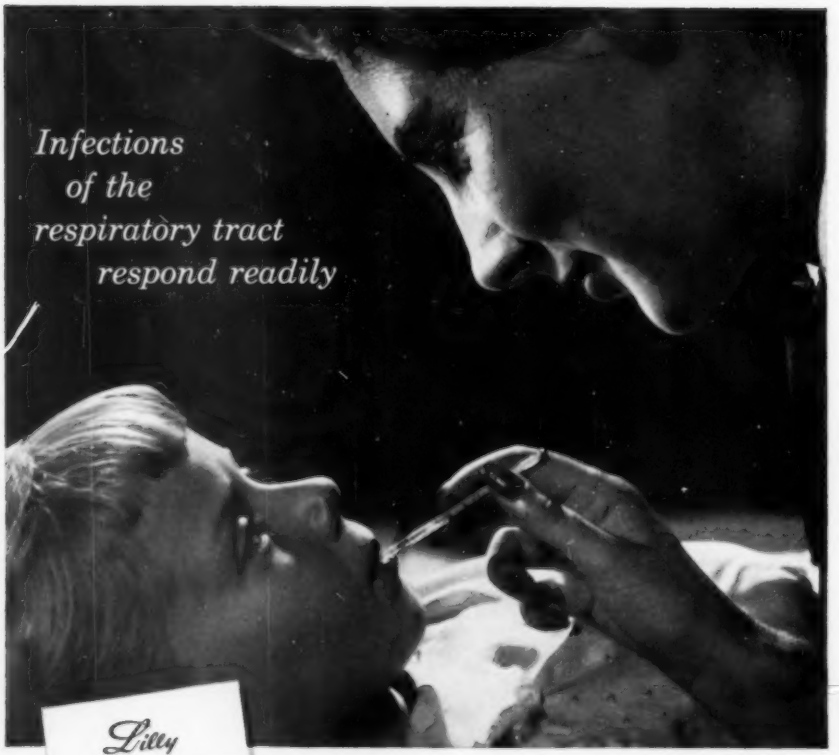


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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

*Published Monthly by* THE NEW YORK ACADEMY OF MEDICINE
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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 32, NO. 11 NOVEMBER 1956

# THE PSYCHOLOGY OF DRIVERS*

HERBERT J. STACK, Ph.D.

Director, Center for Safety Education, New York University

I EXPECT that everyone in this audience at some time or other has taken a driver's license examination. Or it may be that some of you got your license via the so-called "Grandfather Clause." In the early days when state license laws were passed, provisions were made for those who had been driving to get their license without a test. Hence the phrase, "Grandfather Clause." If you did take a license examination and passed it, you may have concluded, "Well, the State Department of Motor Vehicles has approved me as a driver. I must be good." In any case, you can renew your license as you will—even though you took your test 40 years ago.

But, unfortunately, passing that license examination doesn't indicate by any means that you are a good driver. The examination undoubtedly included a simple test of visual acuity, one on laws and regulations, and a short road test. Merely passing such a test simply shows that you met the state's minimum standards for the driver's license. It would by no means signify that you were a good driver. Let us see what we mean by this.

* Presented at the Stated Meeting of The New York Academy of Medicine, February 2, 1956, as part of the Thirty-First Hermann M. Biggs Memorial Lecture, a symposium on *Automobile Accidents and their Prevention*. This program was arranged by the Committee on Public Health.

First of all, take the test for visual acuity. While it does have some value in screening out those with very poor vision, visual acuity in itself is not of great importance in driving. Depth perception, field of vision, and night vision are quite as important, but you were not tested for these. The test of your knowledge of laws and driving practices may have had a little more value, for good drivers tend to be well informed about these things. The third part of the examination, the road test, gave some indication of your skills but told almost nothing about your driving practices.

Thus, the screening process that you have gone through has not revealed the really important characteristics that will make for good or bad driving. It does not indicate anything about your attitudes, your perception, your judgment, your emotional stability, your ability to act promptly in emergencies, and other personal characteristics that have far more to do with your future success as a driver than visual acuity, knowledge and skills. These important characteristics really make up the personality of the driver.

Beginning in 1940, the Center for Safety Education has been conducting a series of studies having to do with the personal characteristics of drivers who are accident repeaters or chronic violators. These studies have been carried on in cooperation with the motor vehicle and state police departments of New York, Connecticut, Michigan, and during the last two years, New Jersey. In each state, driver clinics were organized, and accident repeaters and chronic violators were called in and put through a battery of tests. At the same time, a comparable group of accident-free drivers were given the same tests. I wish there were time to discuss the various types of tests that were used, but these are covered in detail in the reports that have been issued.

What do these studies tend to show? At one time, we had felt that many accidents were caused by deficiencies in certain psychophysical characteristics, such as reaction time, glare recovery time, visual acuity, and the like. But in all of our studies these characteristics have been found to have little significance. The real causes of accidents are far more deep-seated. They have to do with our attitudes, our emotions, and our judgments.

According to Leon Brody in *The Psychology of Problem Drivers*,[1] "Research strongly indicates that problem drivers are problem people—or rather, people with problems, including problems of which they

often are not aware. Thus, the psychology of problem drivers is essentially the psychology of problem people."

Practically all of the studies we have conducted have shown the importance of attitudes. We know that drivers who are discourteous, who are over-aggressive, impatient, and unstable, tend to have a poor driving record. And we know that serious accident repeaters tend to be maladjusted. Studies conducted by Drs. W. A. Tillmann and G. E. Hobbs,[2] of the University of Western Ontario, showed that "accident repeaters were readily distinguished by a personal history of aggressiveness, impulsiveness, and intolerance of limitations on their behavior." Wisely's research at Northwestern University[3] showed that "accident repeaters seemed to act impulsively in many situations, tended to become frustrated in others, and showed an inability to make adequate decisions or choices—quite contrary to what was observed in the accident-free group."

More recently, Brody, reporting on the findings of the New Jersey Driver Improvement Clinic in Trenton,[4] at which 5,000 drivers have been tested in a two and a half year period, concluded, "The problem of safe, lawful, and courteous driving is primarily a problem of emotional make-up and social adequacy. So-called psychophysical functions (reaction time, glare recovery time, and the like) do not, per se, differentiate between good and bad drivers. Other research studies indicate that the following characteristics are evidenced by chronic violators and accident repeaters: They are apt to be aggressive and intolerant of others. They tend to resent authority. They are inclined to have an exaggerated opinion of their importance and their abilities. They are likely to be lacking in responsibility. And often they act impulsively—on the spur of the moment. . . . The basis for such characteristics is likely to be obscure. Just as eight-ninths of an iceberg lies below the surface of the water, so are most of the factors and forces that shape an individual's personality hidden in his background, often going back to early childhood experiences."

I think that you can readily see what this adds up to. In a certain sense, a man drives as he lives—it is one way in which he expresses his personality. If he is the over-aggressive type, you will be apt to find him speeding or switching from lane to lane. The impatient types show themselves as horn blowers; the discourteous, as road hogs; the reckless, as speeders and chance takers.

Consider a single illustration. Let us take the case of an experienced driver who is known to be well informed and skilful. He knows safe practices. One evening he drives out to the country club or a tavern with friends. Radio, television, and newspaper stories have drilled into him the slogan that "alcohol and gasoline do not mix." But he has bad attitudes. He has his drinks, just the same, too many of them, and attempts to drive home intoxicated – only to be involved in a serious accident. The police report the cause as "driver under the influence." But the underlying cause is faulty attitudes.

According to the National Safety Council's *Accident Facts*,[3] in over 80 per cent of the fatal traffic accidents that occur annually, the driver is at fault; he fails to obey regulations or commits some other unsafe act. These unsafe acts are recorded as excessive speed, not having the right of way, under the influence of alcohol, failure to keep to the right, improper passing, and disregarding an officer or traffic control device. When officers visit the scene of the accident, one or more of these may be indicated as the cause of the accident. But, as you can readily see, these are not the true causes–they are only the last physical acts before the accident occurred. They might be called symptoms, but the real causes are deeper-seated. They will be found largely in the personal characteristics that we have been discussing–faulty attitudes like over-aggressiveness, discourtesy, and the like. And to reduce accidents, we must endeavor to remove the underlying causes.

Thus far we have been discussing accident repeaters or problem drivers. It should not be assumed by any means that this relatively small group of drivers cause a large percentage of accidents. While they do have far more than their share, the great majority of accidents are caused by what we call the average driver, even as you and I. Dr. Herman Hilleboe, of the New York State Department of Health, reported a study which showed that 96 per cent of the accidents were found to occur among individuals who were not accident-prone. Another study conducted by the New York University Center for Safety Education showed that up to 95 per cent of all drivers checked were exceeding posted speed limits. Since violations and accidents go hand in hand, it would appear that the large percentage of accidents were not caused by the so-called "problem drivers"–but by the rank and file. This is, in a sense, a national disease of epidemic importance that concerns all of us.

We were very much surprised by a recent report of the Connecticut Safety Commission, covering 294 Connecticut drivers involved in fatal traffic accidents, that 81 per cent had never been involved in collisions, and 68 per cent had histories free of violations or collisions. Very few driving records indicated tendencies of owners being accident-prone or scoff-law. We might call these people average drivers. We cannot blame most accidents on the small group of repeaters.

What are some of the implications of the research that has been conducted on the driver? What use can be made of the findings?

In the first place, as you may know, more than 10,000 high schools and 300 colleges are now teaching driver education, last year giving instruction to nearly one million students. The research findings have been incorporated into textbooks used by schools and college texts, such as *Highway Safety and Driver Education*,[6] used in training teachers. Schools have been urged to emphasize attitude improvement in addition to development of knowledge and skills. Thus, we are attempting to feed back research findings into training programs, not only in the schools but also in programs for commercial vehicle drivers.

In the second place, we are urging that each state set up some type of clinic in connection with point systems. These are primarily for studying repeater cases and attempting to rehabilitate them. You may know that plans are being drawn up for such a clinic in New York State. As drivers become serious offenders, they will be called into this clinic and given various tests to determine their weaknesses with a view to correction.

Another use for the findings is in traffic court schools, such as the one now being operated in connection with the New York City traffic courts. Also, supervisors of commercial fleets who are in charge of truck and bus drivers are very much interested in research on accident repeaters and chronic violators. Accidents can be very costly to motor transport and bus companies. That is why more than 30 colleges throughout the country are conducting training courses for supervisors and driver trainers of fleets. These courses include a discussion of how to deal with the repeater problem through examinations, hearings, and retraining of drivers. Indeed, the better commercial fleets are making more use of research on the driver than many other agencies.

Of course, the most important possible use of research findings is in improvement of driver license tests in the states. This is going to be

a difficult task, for the simple type of license examination has been used for over 20 years and it will be hard to make changes. Another problem lies in the fact that only a limited time, perhaps 15 minutes, is now used for tests, and any program that we might suggest would require at least that time for psychological testing alone. It is extremely difficult to get at personal characteristics of drivers in short tests.

A number of states have been considering inaugurating a program of periodic reexamination of drivers, perhaps every ten years. If this were to be done, the typical tests now used for the original screening would be of little value. Such tests might locate a few drivers whose vision had been impaired, but would not get at the really important characteristics that are directly related to accidents. New tests need to be standardized that will get at attitudes, judgments, maladjustments, emotional stability, and the other personal factors that we have been discussing in this paper. We frankly admit that we do not have such tests at this time.

Naturally, prevention of traffic accidents is to be preferred over cure. The ultimate solution of the problem lies in education rather than in reeducation or correction through enforcement. But we are still going to urge a strong enforcement program for good enforcement tends to improve driver attitudes.

Our basic goal, then, is to develop among drivers a kind of sense of social responsibility and the emotional stability that are so important to safety in everyday driving. Our chief support in this move is going to be obtained through the work of the schools and colleges.

A final word regarding the relationship of the patient with his doctor. The doctor-patient relationship is a close one; the doctor is a counselor, confidant, and friend. What can he do to advise his patient regarding driving? In the case of both acute and chronic illnesses, it is suggested that physicians advise their patients of any condition—and that covers drugs and chemicals used in treating these illnesses—that may endanger their safety on the road. There are many more illnesses and disorders than are commonly realized that may lead to accidents. We know that epilepsy and heart conditions can cause momentary lapse of consciousness. We know that certain antihistamines, sedatives, and other drugs can lower the efficiency of the driver. We know that certain emotional conditions may affect his performance. Medical authorities can spell out the importance of specific illnesses and disorders in relation to safety on the road.

It is for this reason that detailed plans are being prepared for a one-day conference to be held in May of this year on "The Medical Aspects of Motor Vehicle Accident Prevention." This will be co-sponsored by the New York University-Bellevue Medical Center, the Center for Safety Education, and medical societies in the metropolitan area. Leaders in traffic safety, especially those in driver license departments, want to get the advice and guidance of the medical profession regarding the significance of various illnesses and disorders. They also want to get the interest and support of doctors to aid in the overall attack on accidents. You will hear more about this conference at a later date.

The task of striking at the increasing toll of traffic accidents is a tremendous one. It needs the support of all community forces. There is much that the medical profession can do to help.

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# THE EPIDEMIOLOGICAL ASPECTS OF AUTOMOBILE ACCIDENTS*

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NEVER before in history has any nation been able to provide so many social and economic benefits to its individual citizens as present day America. The provision of these benefits is, to a very large degree, the result of our ability to move both people and the goods we make more rapidly through our advanced system of transportation and communication. There is no doubt that the outstanding characteristic of our method of living is its mobility. In truth, the common denominator of all citizens of our nation, other than the income tax, has become the passenger automobile. In 1946 this nation had approximately 37 million passenger vehicles on its highways. By the end of 1955 this figure had risen to 52 million passenger vehicles. This common denominator of the transportation world has evolved from a pleasure car to the most essential single instrument of our entire pattern of living. Its abrupt removal would create economic and social chaos.

With all the benefits which the passenger automobile has brought us and the pattern of living it has let us establish, it has also brought with it a dangerous by-product. This by-product should be classified as a mass traumatic disease which is producing pathological results for approximately one million two hundred thousand of our citizens *each* year. Evaluation of the data covering the year 1952, which were released in 1954 by the Bureau of Vital Statistics of the U. S. Public Health Service, provides interesting information as to the importance of this mass disease, as a cause of death, in comparison with other disease entities.

When the 17 leading causes of death are ranked in order of the percentage of the total living population affected by these diseases, the highest incidence of fatal disease in the ages 5 through 34 is found to be

* Presented at the Stated Meeting of The New York Academy of Medicine, February 2, 1956, as part of the Thirty-First Hermann M. Biggs Memorial Lecture, a symposium on *Automobile Accidents and their Prevention*. This program was arranged by the Committee on Public Health.

accidental deaths. By separating accidental deaths from all those deaths attributed to accidents in motor vehicles, we observe that the modern passenger car is the third leading cause of death in ages 5 through 9, the second most frequent cause of death observed in the ages 10 through 14, the foremost cause of death in the ages 15 through 19 as well as 20 through 24. The motor vehicle moves back to the second most frequent cause of death in the 25 through 29 age groups, the fourth ranking cause of death in the 30 through 34, as well as the 35 through 39 age groups. Thus it may safely be said that in the ages 5 through 39, the passenger vehicle will be seen as one of the most likely items to produce death among our population.

This same rank in cause of death may be observed if the U. S. Public Health Service's data are examined from the point of view of the percentages of fatalities represented by the 17 causes of death. However, the true scope of the problem of trauma produced by the motor vehicle must not be evaluated by merely looking at data on fatalities. While approximately 38,000 fatalities in passenger vehicle accidents have been observed each year for the past 20 years, estimates produced by the National Safety Council indicate that injuries have consistently exceeded one million two hundred thousand. Additional data from this latter source lead us to believe that at least one hundred thousand of these more than a million injuries result in permanent disability each year.

From the point of view of epidemiology and mass disease problems, this must be accepted as the true scope of the price we have been willing to pay for the mobility which the passenger automobile has brought.

For too long, too many groups have been willing to concede that injury and death were the inevitable price of accidents and because of the complex cause factors, associated with the production of these accidents, there was little or nothing that could be done unless we could develop techniques for preventing people from making mistakes in judgment while operating mobile equipment.

A small research group in the Department of Public Health and Preventive Medicine at Cornell University Medical College has been gathering data which could be useful in examining the cause of injury as differentiated from the data which seek to establish the cause of the accident. These data have conclusively demonstrated that the accident, per se, does not produce trauma. Data published as far back as 1942 in the Bulletin of War Medicine pointed out that many cases of very minor

injury were observed in studying accidental falls or attempted suicide jumps from heights varying from 50 to 150 feet, while many deaths were observed from falls from no more than 5 feet. These early data suggested, and subsequent research confirmed, that the degree and extent of injury in accidents are determined by three factors: 1) Peak load of force and its time of duration. 2) The distribution of force over the body area. 3) Rate of onset of this force.

It has been established that human biological tissue will survive with moderate injury forces that reach levels of 100 units of gravity (100 times the body weight of the individual being studied), if the force of stopping the body is not applied for periods longer than one-tenth of a second and if the absorption of this force is spread over a wide body area. It was also observed that the shape and construction of the object being struck by the body had very great influence in determining the seriousness of injury.

There is little doubt that medicine and its allied sciences are most qualified to apply the scientific disciplines necessary for studying this mass traumatic disease seen in motor vehicle accidents. If the proper quality and quantity of data can be gathered, it is known that meaningful correlations can be established between the host who has "traumatic disease" (occupant of the passenger vehicle), the agent which produces the disease (the items observed in the interior of the passenger vehicle), and the environment in which the disease is acquired (the highway or street where the accident occurs).

This approach has been singularly successful in the past in producing solutions in such mass diseases as bubonic plague, typhoid fever, malaria, yellow fever and others. In the case of each of these diseases, once the epidemiologist has demonstrated positive correlations between the host, the agent and the environment, it has been possible to initiate a program of altering or controlling those factors which relate to the agent or the environment so that the host does not continue to have the same degree of exposure. In this current "mass disease" associated with impacts in automobiles, it is possible for medical research, using the tools of epidemiology and biological statistics, to find those items which stand most in need of change. The design engineer and manufacturer can then make changes which should lead to a calculated reduction in the frequency and severity of injury or death observed during the impacts. Meanwhile, the search is continued for practical solutions to the complex

mistakes in human judgment which, at present, must be conceded to be the primary cause of motor vehicle accidents.

An epidemiological approach has been undertaken with the cooperation of medical societies, state departments of public health, and state police groups of North Carolina, Virginia, Maryland, Connecticut, Indiana, Minnesota, Texas, Arizona, California, Vermont, Pennsylvania, and the City of Minneapolis. With carefully designed standardized data gathering forms, the enforcement officers and the medical profession are contributing data from this "laboratory of the highways" to the Automotive Crash Injury Research group at Cornell, where a standard technique of evaluation and analysis is employed to identify the characteristics of the agent and the environment which are causing injury as well as death to the host. This new approach, which is a very practical supplement to the excellent work being done in the field of preventing the accident, has been sponsored by the Commission on Accidental Trauma of the Armed Forces Epidemiological Board with funds supplied by the Office of the Surgeon General of the Department of the Army, the Division of Research Grants of the National Institutes of Health, the Department of Health, Education, and Welfare, and by very generous grants by the Ford Motor Company and the Chrysler Corporation. The data collected have been utilized by automobile manufacturers in this country as a basis for evaluating the necessity of redesigning those components of the automobile which can be identified as possessing the highest frequency in causing injury during the accident.

With the introduction by some automobile manufacturers of new door lock designs, energy absorbing steering wheels, specially designed energy absorbing padding on instrument panels and forward overhead structure, as well as safety belts, the epidemiological approach can now also be used as an objective measuring device to determine the degree of reduction in both the frequency and severity of injury that these changes are providing.

Each engineering change affecting the agent's ability for producing trauma, must be measured to determine the degree of improvement each represents in order that revisions, as well as changes, may be added in an effort to successfully attack the mass disease which so affects the American citizen's most useful instrument, the passenger vehicle. The successful continuation of the present teamwork between medical research and an alert and progressive minded automotive industry promises great hope for the future in controlling the mass disease problem which is an outstanding characteristic of our social and economic way of living.

# TRAFFIC CONDITIONS*

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MOTOR vehicular transportation, which has been a blessing to the advance of American civilization, has become both an economic affliction and a humanitarian challenge to the American people. Traffic conditions can readily be divided into two categories for purposes of analysis. One section is that relating to the movement of vehicles on streets and highways—a technological problem as far as the basic elements of mobility and facility are concerned. This portion of the problem is a nightmare to the automotive, highway and traffic engineers, who struggle with the congestion of 60 million vehicles on streets and roads mainly inadequate for safe, smooth and efficient transportation. The present complexity of solutions is not made easier by the forecast of 120 million vehicles in the United States in another 20 years.

Everything which the engineer may do to improve traffic conditions is designed, ultimately, to serve the highway user. It is the performance of this highway user, as driver, passenger and pedestrian, which delineates the second section of the traffic problem. In this portion we face, squarely, the fact that human behavior has made of our automotive civilization a mixed benefit and harm—a benefit in transportation economics and recreational opportunity, but a harm in the sorry spectacle of death, injury and destruction of property which accompanies vehicular movement.

Great minds and great organizations have tangled with traffic accident prevention for many years, but a candid appraisal tells us that we have made little lasting progress in the reduction of traffic casualties. Plainly, decisive and perhaps even heroic measures are needed to bring our traffic tragedy under control. Many of these steps must be new, for most of the methods we have employed have been a case of "too little" or too poor an aim to strike at basic causes. That something new is

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needed is carved, forever, on the headstone of the traffic blight which was 1955—the second highest highway death toll since the advent of the automobile.

Where are the so-called experts who should be working, ceaselessly, to develop methods of determining who may drive—methods designed for the capabilities and the probabilities of today's driver using today's motor vehicles on today's highways, with more than lingering consideration to the needs of tomorrow?

I suspect that some of the experts are trying to find a new way of telling a shocked nation that, although we killed more people on our streets and highways last year than in any other year save one, we did it while the traffic fatality rate was the lowest in history, so we have something for which to be thankful. I suspect that others are trying to reconcile 38,800 deaths with the assertion that some of the best techniques of traffic law enforcement—scientific methods such as radar speed control and chemical tests for intoxication—should be outlawed because they are unfair to the motorist or are an invasion of his personal liberties. And yet another group is, I believe, pouring over the drafting table figuring how many more horsepower they can tuck under the hood of the 1957 model cars while denying that the horsepower sweepstakes has any psychological impact on the behavior pattern of 72 million licensed drivers.

Few of the experts are probing the role of the human being in highway safety. The human being—who is the neglected element in the automotive transport formula. The human being—where we have not produced one new model over the years in which mechanization has moved from one cylinder to twelve and highways from an Indian trail to the Ohio Turnpike.

If I were asked to summarize, in one sentence, my frank belief as to why we continue to kill and maim on our streets and highways, I would say that it is because man has not kept pace with the automotive technological progress which is his own creation. The only way in which we could have kept pace with change would have been to adjust our concept and operation of driver control to man's changing viewpoint and to the advance of automotive technology. Failing in both, we must now recoup our losses, meet the present challenge and plan ahead. To understand traffic conditions we must, I believe, understand thoroughly the conditions surrounding our two points of basic impact on why peo-

ple do what they do as drivers.

Our driver is what he is because we have conditioned him to "take a chance" rather than to "play it safe." We may not have been conscious of the fact that we were building this mass attitude among a large proportion of our drivers, but a little exploration will uncover the contributing factors.

*First* is the element of *growth*. There's an old New England expression which says that a man is "too big for his britches." Well, we have ample evidence that modern highway transportation is "too big for its britches." We are all aware that we do not have the modern roads to accommodate present traffic flow needs. Perhaps more important is the fact that our methods of preparation for the driving privilege and our legal determination of who may drive have not matched the gains in either the number of vehicles or the number of drivers. The foundation for this lag was written in the very origin of driver and vehicle licensing. Both came into existence for revenue rather than control purposes and, after nearly five decades, this is where the licensing function remains in the laws of many states and in the viewpoint of many legislatures. In some of our biggest jurisdictions, notably New York and Pennsylvania, the licensing authority is still a wing of Taxation and Finance or of the Department of Revenue, biennially barred from effective driver and vehicle control by lawmakers who are fearful of public reaction to a policy of strict, impartial traffic law enforcement and motor vehicle administration.

In passing, let me say—don't entirely blame the public officials charged with the legal responsibility for driver licensing for the conditions which exist today. The motor vehicle administrator of 1956 knows what he needs to do a maximum job of effective driver control. His problem is how to get it. Remember, he is only an administrator. He can recommend, but he does not make the laws or appropriate the funds for their prosecution.

Similarly alert to the need and equally handicapped are the agencies of traffic law enforcement. Our state and local police departments are, for the most part, undermanned, undertrained and underpaid to do their assigned task in traffic control. On a national average we have only one state patrolman for every 170 miles of paved rural highway. To meet the accepted standard of one for every 50 miles of highway it would require, as of today, 28,084 more state troopers in the United States.

Finally, in high school driver education, since the first courses were introduced in Bergen County, New Jersey, 25 years ago, we have reached the point where driver education is offered by half the nation's public high schools and reaches 62 per cent of the eligible pupils. Unfortunately, far too many of the courses are sub-standard as to time and quality. Yes, we have progressed, but not fast enough to meet the growth of vehicles and drivers.

Closely allied to growth is a *second* factor which I will label "*the American urge*." We have glorified our national proclivity to do things more quickly and better than any other group of people on the face of the earth. Sometimes this ability has been our salvation. In two World Wars, starting with substantially nothing, we have machined the materiel of manpower and equipment with sufficient rapidity to save ourselves and the world from disaster. But this national "urge" translates itself into a constant attempt to live up to the creed that we can be "fastest and firstest with the mostest."

We see and hear the evidence of this urge every day. A production manager boasts that his "Excelsior Safety Pin and Snap Fastener" factory has doubled its output and now manufactures more "hookanannies" than any other plant in the world. We are desolated at the possibility that our American athletes may not attain the top team score in the Winter Olympics. It makes no difference whether the item be agricultural, mechanical, physical or social, we have a goal of "more, better and faster."

In reasonable doses we need the spirit and drive of "the American urge" but when we transfer this urge to the highways of our country, the desire to get there "firstest and fastest" produces nothing but trouble. In the factory it may be efficiency—on the highways it's dangerous. On the farm it may be a boon to mankind in increased food production—on the highways it's a hazard. So our urge for speed, built into the habit pattern of the American people by its perpetual glorification, proves to be a trap when applied to the commonplace of the motor vehicle on the public highway. In this urge we have made a fetish of the clock—rushing to catch the 7:43 train, the 8:10 bus, to make our next appointment, to be there for the start of the show or the game. Once we would ask: "How many miles is it from New York to Great Barrington?" Now we say: "How long will it take me to drive to Great Barrington?"

The *third* factor which I see I will call "*technological pampering*."

In spelling out the details of this element I must say that I recognize the necessity for mechanical progress. It would be unthinkable to contend that we would have safer highways if 4-wheel brakes had never been invented. On the other hand, I do contend that while technology has provided the mechanical progress we have done little or nothing to match it with human progress and, as a result, have pampered the highway user into a false Utopia of highway safety security.

Our engineers have built safety into our highways. We have learned a lot about channelization, grades and curves, limited access and scores of other design and construction techniques since we first drove over washboard gravel in Vermont or slid off high-crowned black-top in northern New York. The accident experience on the old type roadway led us to remove the traffic booby traps from the path of the irresponsible. Our automotive engineers have created devices to relieve the tedium of braking, steering, light dimming or even turning a crank to raise or lower the windows. In net result, we have provided an environment more comfortable than their living room for many drivers. We've told these drivers that the environment was safe because we made it so with our technological know-how. In too many cases, all we have done is belittle human intellect as being responsible for human action. The safety feature of the vehicle and the highway does not pass, spontaneously, to the human brain.

Unhappily, when we design a highway to accommodate 70 mile-an-hour speeds, there is nothing to prevent a 25 mile-an-hour brain from using that highway—and with an admitted design for 70, there is always some jackass who must try the curves at 90. As long as the top figure on the speedometer face is 120 or more, then just so long will we have state police officers making arrests for 118 and 126 miles-an-hour when some tempter of fate tries to push the needle or the disc to the top of the dial. In short, all the mechanical safety devices we can engineer go for naught when human intellect refuses to capitalize on them and plunges headlong into an accident producing situation.

Strange, indeed, have been some of the methods of safety promotion which contributed to the viewpoint of the people toward driver responsibility. Let me cite an example.

The "American urge" for "firstest and fastest" is planted, nurtured and ripened in the contention of organizations and individuals that we should have one code of ethical conduct for the highway users and

another code for the enforcement officers. We once joked about the motorcycle officer hiding behind a billboard and, under the guise of fair play, we said that this technique, or that of using unmarked police cars, was un-American. Why? If the traffic law violator *is* a menace to the public welfare and we want him removed from the highway, what's wrong with apprehension in an unmarked police car? All any driver needs to do to avoid entanglement with the law is to live by the rules. When the rules of good driver behavior are violated, the culprit is already far outside any known pattern of fair play. Why must the police be more ethical in their assigned task of public protection? The fair play fantasy only serves to sustain an elaborate game of "cops and robbers" in traffic law enforcement. In the days of six-shooters and a handsome white steed, the game had romance. Now it has only the crash of metal against metal and the agonized screams of the dying.

Here is still another example of an influence on both public attitude toward highway safety and the individual performance of drivers. Early in December, one of the major automobile manufacturers ran full-page newspaper advertisements which proclaimed, of a 1956 model: "At 50 it's using only 10 per cent of its horsepower." Now the automotive engineer can tell me that the relationship of horsepower to speed is not constant and I'll agree. At the same time, I will submit to any impartial judgment a broad interpretation of the statement: "At 50 it's using only 10 per cent of its horsepower." To the would-be owner of this vehicle, conditioned from birth to the glories of speed, the message only says: "Brother, imagine what it would do if you used 100 per cent of its horsepower."

On January 2, broadcasting one of the Bowl football games, the same manufacturer was telling us of the same car, that the 1956 model brakes were so good that it could "Stop on a Dime." In high school driver education and in motor fleet safety training we reach a little over one million drivers a year. Our trained teachers, using carefully executed demonstrations, show that even at 25 miles-an-hour it requires 67 feet to stop a passenger car, while at 55 it requires the length of a football field. How puny is our effort to reach a million people with the safe side of vehicle stopping when the "Stop on a Dime" falsehood pours out of our television receivers and reaches an audience of 30 to 40 million. Unhappily, too many of that audience will be foolish enough to believe the statement.

When all of the influences are put together, what is the viewpoint of the American people toward the motor vehicle and toward that small piece of paper which attests the legal privilege of operating that vehicle? Horatius may have guarded the bridge and Hercules the Gardens of the Hesperides. Vestals may have protected the sacred flame and a dragon the Golden Fleece. They were pikers in comparison with the struggle of the average man in the mid-Twentieth Century to preserve the right to own and operate a motor vehicle. You may note that I have changed terminology from privilege to right. I did so with intent, because too many of our drivers have lost sight of the privilege concept and regard the driver license as an inalienable right guaranteed every free-born American under the Constitution and the Bill of Rights. Second only to the sanctity of man's home as his castle is the fierce pride in the possession of an automobile and all that it means in terms of business, recreation and mobility.

I cannot outline all the steps needed to end safety's deadliest race—that of education versus automation, but I do want to conclude with a look at one step which must be the foundation for all others.

In driver licensing we have the opportunity to determine who can keep pace or who has kept pace with the strides of automotive and highway technology. As the psychologists point out the traits of chronic violators and accident repeaters on the highways, and as we obtain more universal recognition that an unsafe performance on the highways is an act of anti-social behavior, we must also realize that there must be some way to discover these tendencies in advance and to predict their relationship to driving performance. Beginnings have been made in this direction by the transit industry and in driver selection for motor truck fleet operations. There are even conclusions which can be drawn from psychophysical testing which verge on the definite plotting of an accident and violation probability. Such testing has not been used in enough cases on the broad scale of state license examinations to be sure of its validity. Moreover, there are serious lacks between what we want to know and the tests available to find the answers.

It would be wishful thinking to expect that states will turn, easily, to driver licensing based on thorough mental, emotional and physical testing without debate over the accuracy of the tests and the rights of the individual. Sooner or later such testing must come if we are to allow only the fit to drive. We can hasten the day if scientists who command

universal respect will establish and recommend the pattern. It appears certain that many of us haven't the reactions and the perception to cope with the high speeds allowed on the superhighways of 1956. With more new superhighways engineered for safety and more vehicles of greater horsepower, we will widen the gap between human and mechanical ability. So the development of new testing methods, discovered or created solely for driver licensing purposes, is a must of our highway safety future. We will find these methods only through extensive research and patient experimentation. The quest is impossible unless we can assemble the best minds in the fields of testing, psychology, psychiatry, medicine, education and safety to plan, direct and conduct this work. Such a program requires money—not a few thousand dollars but several millions. I can't believe that we haven't the ability to develop tests which will rule dangerous drivers off the road before they ever have a chance to menace persons and property. In education and industry we have produced tests of aptitude, attitude and intelligence which will chart, with certainty, the strength and the weakness of the would-be student or worker. We can do the same thing for the driver when we are ready to make the effort.

This will be a bold program and it will encounter tremendous opposition. It requires no gifted sociologist and no avid student of jurisprudence to know that our social, ethical, moral, legal and even economic adjustments lag far behind our ability to discover, create and produce new things. This was true in the Industrial Revolution, it is true in the Atomic Age, but only a few people are ready to admit, belatedly, that it is also true in the Automotive Era. To eliminate this lag in the field of highway traffic, complete testing to determine who may drive is wholly realistic. It involves no "Buck Rogers" technique and no cosmic formula. It is based on new development of methods we already know. It's another challenge to cure a human ill.

In a half century we haven't solved the traffic accident problem by preachment, punishment, warning, fear, rehabilitation or mechanization. I am convinced that we haven't applied enough of some of these precepts, particularly in the field of enforcement. I am equally convinced that it's time we stepped bravely up to a new human engineering approach with determination, courage and no expectation of failure. When we win we will have eliminated the most prevalent form of man's inhumanity to man.

# TOXIC EFFECTS OF THERAPEUTIC AGENTS

*Transcription of a Panel Meeting on Therapeutics**

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* Presented at the Monthly Panel Meeting on Therapeutics (Fourth Series) at The New York Academy of Medicine.

MODERATOR PAUL REZNIKOFF: The subject of this Panel Meeting is "Toxic Effects of Therapeutic Agents." It is quite obvious that we cannot cover all of the toxic effects of all therapeutic agents and, therefore, in the limited time we have, and because we wish to allow some time for questions, our speakers will stress only some of the outstanding problems in this field.

I will introduce the members of the Panel: Dr. Harry M. Rose, John E. Borne Professor of Medical and Surgical Research at the College of Physicians and Surgeons, Columbia University and Executive Officer of the Department of Microbiology at that institution, as well as Attending Microbiologist at Presbyterian Hospital. He will talk to us on the subject of the general effects. Dr. Marvin Stern, Associate Professor of Clinical Psychiatry, at New York University College of Medicine and Associate Visiting Neuropsychiatrist at Bellevue Hospital, will discuss the neuropsychiatric aspects. Dr. Louis R. Wasserman is Director of the Department of Hematology of The Mount Sinai Hospital of New York, and he will tell us about the toxic effects of therapeutic agents on the hematopoietic system. So without any further delay I shall first call upon Dr. Rose.

DR. HARRY M. ROSE: This is an extremely broad topic, and it is impossible to cover it in the time allotted, even though Dr. Reznikoff has instructed me to forego any discussion of toxic effects which result in blood dyscrasias or psychiatric disorders.

What do we mean by toxicity? Certainly we do not refer to the narrow region defined by the strict meaning of the word, coming from the Latin *toxicum*, a poison, which is itself derived from *potio*, a dangerous draught of liquid with direct noxious effect. I think that toxicity would best be defined in this discussion as the undesirable effect of a therapeutic agent which differs from its expected action and is harmful to the patient. With this definition in mind, it is clearly possible to consider toxicity of therapeutic agents from two main points of view:

1. Toxic reactions which are related to their direct effects on physiological processes; and

2. Reactions caused by indirect effects of the agents, generally as the result of an abnormal response by the recipient.

As an example in the first category we may cite morphine, which is well known to cause toxic reactions if the proper dose is exceeded, and in the second category, penicillin, which can cause severe or even

fatal anaphylactic reactions in patients who have become hypersensitive to this antibiotic.

In general, leaving aside those reactions which involve the hematopoietic system or provoke psychiatric disturbances, toxicity is manifested by signs and symptoms referable to the nervous system, liver, kidneys, cutaneous tissues, and gastrointestinal tract, or by systemic phenomena of which fever is the outstanding example.

Since it is obviously impossible to discuss all therapeutic agents, I am going to confine my subsequent remarks to drugs which have been more recently introduced, and particularly to antibiotic or chemotherapeutic compounds.

First, with respect to the direct toxic action of these agents, a few examples may be noted. Sulfamethylthiazole, one of the earlier sulfonamide drugs, frequently caused peripheral neuritis and this untoward and often serious side effect soon led to its exclusion from clinical medicine. I mention this primarily to emphasize that minor alterations in the basic structural formula of a drug may be profoundly important in determining the character of the toxic reactions it produces.

Another interesting example of a toxic effect apparently due to the direct action of the therapeutic agent is the neurologic disturbance caused by stilbamidine. This drug, as you know, has been used in the treatment of trypanosomiasis, leishmaniasis, multiple myeloma, and systemic mycotic infections, especially blastomycosis. The administration of stilbamidine for a period of several weeks frequently results in anesthesia of the area innervated by the sensory division of the fifth cranial nerve. It is of interest to note that the same sort of regional anesthesia is produced by the inhalation of trichlorethylene. These two drugs would not at first seem to have much in common, but it so happens that stilbamidine is the only member of the diamidine group that contains an ethylene linkage, and it is generally conceded that the peculiar effect on the sensory division of the fifth nerve is the result of this chemical configuration which is in some way concerned with the neurotoxic effect.

Many therapeutic agents can cause direct toxic effects on the kidneys, and one example is bacitracin which, as you know, in ordinary therapeutic dosage often causes a mild degree of albuminuria. If larger doses of the drug are given or if the drug is continued for too long a period, albuminuria may become excessive, nitrogen retention occurs,

and a nephrotic syndrome may be produced. The same type of phenomenon, developing even more acutely, may be seen following the administration of any one of the polymyxins. These antibiotics likewise are capable of producing neurotoxic effects by their direct action, usually in the form of paresthesias involving the hands, tongue and the circumoral area. All of us are familiar, of course, with the direct toxic effect of streptomycin and dihydrostreptomycin on the eighth nerve, and I need not elaborate any more on that particular point.

Another very interesting toxic effect which results, probably from the direct action of the compound, is seen following the administration of hydralizine (Apresoline), a drug which is commonly and often rather unwisely used for the management of hypertensive vascular disease. It has been noted, especially in those patients who have been given large doses of Apresoline for relatively long periods of time, that a peculiar rheumatoid state characterized by fever and arthralgia makes its appearance. This rheumatoid state may develop ultimately into a clinical syndrome, which is indistinguishable from that seen in disseminated lupus erythematosus.

Most of the toxic reactions to therapeutic agents, however, are indirect and these are mainly due to sensitization on the part of the patient. An outstanding example is hypersensitivity to penicillin. Toxic reactions to penicillin may be of varying types. One of the commonest forms is a dermatitis, which is often mild but may be severe. In more severe reactions the eruption is sometimes urticarial, in other instances the lesions simulate those of erythema nodosum, and in very severe cases there may be an exfoliative dermatitis which can be serious or even fatal.

Another type of reaction to penicillin is a serum sickness-like disease which is characterized by urticaria and arthralgia, usually associated with fever, and often accompanied by leukocytosis with an eosinophilia.

We are all familiar with the fact that sensitization to penicillin may result in severe or even fatal anaphylactic reactions.

Fever as the sole toxic response to penicillin may also be observed. This usually develops in from six to ten days after initial administration of the drug, and it is generally believed that this lag period before the fever first becomes manifest represents the interval required for the formation of antibodies by the patient.

In connection with these various types of toxic reaction to penicillin, it is worth noting that skin tests are of relatively little value in determin-

ing whether a patient is or is not sensitive to the antibiotic. A definite history of sensitization, on the other hand, is important, although there are many instances where it is possible, if the drug is given cautiously, to administer penicillin to patients who give a history of sensitivity. In cases of this sort the drug must be administered with extreme caution at first, and injections should always be made in one of the extremities so that a tourniquet can be applied, if necessary.

Reactions to streptomycin, in addition to the neurotoxic phenomena already mentioned, occur relatively often, and generally consist either of fever, skin eruptions, or of a combination of the two.

Para-aminosalicylic acid also frequently causes side effects, chiefly consisting of fever and cutaneous eruptions. In certain instances a very peculiar picture simulating infectious mononucleosis has been seen following the administration of this drug.

It is fortunate in the case of isoniazid that toxic reactions are extremely rare. When they do occur they generally assume the form of a peripheral neuritis, and it has recently been reported that this toxic neuritis probably results from the fact that administration of isoniazid increases the excretion of pyridoxin. It has been shown that peripheral neuritis caused by isoniazid can be prevented by adequate doses of pyridoxin or vitamin $B_6$.

The tetracycline derivatives and chloramphenicol rarely produce allergic reactions, but such reactions have been reported and have mainly consisted of skin eruptions, either urticarial or eczematoid in type, or resembling erythema multiforme. In some instances fever has been described as well as a serum sickness-like illness. However, most of the so-called toxic effects of the broad-spectrum antibiotics can be related to their action on the bacterial flora of the gastrointestinal tract, and the changes in the bacteria which they induce are frequently followed by distressing symptoms in the patient. One of the common consequences is diarrhea in which it may be found that Monilia have largely replaced the normal bacterial flora of the bowel. In other instances the enterobacteria may be almost entirely supplanted by staphylococci, sometimes leading to a severe and at times even fatal enterocolitis. In addition, members of the genus Proteus and Pseudomonas often represent the replacement flora in the lower gastrointestinal tract of persons receiving broad-spectrum antibiotics, and secondary infections with these organisms are by no means uncommon.

In connection with the sulfonamides we may note in passing that they are not used so frequently as they were formerly, and that the drugs now currently employed are chiefly sulfadiazine and Gantrisin, which rarely produce toxic side effects. When side reactions occur they generally consist of a febrile disturbance, skin eruption, or a form of serum sickness-like disease.

Leaving the antibiotics and chemotherapeutic agents, I would like now to point out that the administration of chlorpromazine has been frequently reported to be associated with a peculiar type of hepatic disorder. Patients under treatment with chlorpromazine may develop jaundice, and liver function tests have indicated that the jaundice is of the obstructive type with elevation of the serum alkaline phosphatase, a rise in serum bilirubin mainly of the direct variety, and an increase in BSP (Bromsulphalein) retention. The cephalin flocculation reaction is usually negative and the thymol turbidity test gives variable results. Many patients with a toxic reaction to chlorpromazine of this type have been operated on for obstructive jaundice with the mistaken diagnosis of mechanical obstruction in the biliary system. A similar hepatic disorder has been noted previously in patients who have been given arsphenamines, methyltestosterone, and, in rare instances, thiouracil. It is believed that hypersensitivity is the responsible mechanism.

Lastly, I would like to make one brief reference to rauwolfia, merely to point out that in some instances this drug may cause sodium retention, and that its administration may lead to edema and congestive failure in patients with an established cardiac condition.

MODERATOR REZNIKOFF: Thank you, Dr. Rose.

We will next hear from Dr. Stern, who will talk to us about the psychiatric aspects of this subject.

DR. MARVIN STERN: For purposes of focusing the discussion a little more sharply, I would like to talk only about those major psychiatric reactions sometimes associated with the use of some drugs, namely, the psychotic reactions, and direct most of my attention to the so-called organic psychotic reactions which tend to fall into two main groups: acute psychoses, which go by various other designations familiar to you, namely, the acute toxic reaction, or acute delirium, or the so-called toxic infectious psychoses; and the chronic psychoses which are also produced by many of the same agents which produce the acute picture.

In considering the symptomatology of the acute psychotic reactions

there are certain aspects which might be highlighted. First, there is a clouding of the consciousness; there is an impaired awareness of what is going on around one; and the attention to the outside surroundings seems to vary a great deal; orientation for time, or person, or place is also irregularly and variously involved but always is involved in these acute psychotic reactions.

Secondly, they present visual and auditory hallucinations as fairly common concomitants of their psychoses.

The third factor which is quite significant is that these patients usually demonstrate marked emotional lability and as a general rule, tend to show marked anxiety.

The fourth factor is in terms of aberrant motor behavior. The motor behavior of these patients may show anything from gross tremors, such as characterize delirium tremens, to movements which are purposeful in dealing with their psychotic ideation.

In contrast to the rather florid picture as presented by the acute psychotic reactions, the chronic reactions are characterized by a much more serious memory impairment, usually greater for recent than for remote events, and by a general intellectual deterioration.

I think it is important to point out at this time that both sets of changes can be produced by a great variety of drugs and I would like to list them now and discuss them a little later when we present some of the problems and evaluate some causes of these changes.

In general, the first group might include the central nervous system depressants. As a group, the barbiturates and bromides are well known to produce psychotic reactions; the morphine group to a much lesser extent—and this I will discuss a little later. Dr. Rose has mentioned reserpine; and recently the literature has cited numerous examples of depression following its protracted use. This is not an organic psychosis but rather a functional reaction. In the group of central nervous system stimulants, amphetamine would be a good example. Autonomic drugs which are known to produce psychotic effects are atropine and scopolamine. The antimalarials also have been known to produce psychotic reactions, and these would include quinine and atabrine. The heavy metals, such as mercury and arsenic, carry their own characteristic picture. Because of their importance in producing psychotic reactions, the steroids deserve special mention.

I would like to point out that, insofar as the diagnosis of these psy-

chotic reactions is concerned, in terms of predicting what agent is responsible for the particular psychotic reaction, the psychiatric picture is far less of a guide to diagnosis than are the laboratory findings which usually make the differential diagnosis.

The first question which usually is raised in evaluating these various states is: Are these reaction types for different drugs distinguishable from the others? Before we go into that I should like to mention that ordinarily the psychotic picture is described under two major headings, namely, what is the form of the psychosis; and secondly, what is its content? By form of psychosis we ordinarily mean, "Is this the picture of an acute delirium, is this a stupor, or is this a wildly hallucinated individual, or one who retains his orientation?" etc. By content we mean what is produced as verbalizations by the patient during the course of this particular disturbed episode. I think it is important to point out that all of the investigators who work with these psychoses feel that the form and content run a course independent of the inciting agent so that these would not be particularly helpful in making a differential diagnosis.

What factors are involved which influence the reaction? First, is the intensity of biologic disturbance. Apparently those patients who are more seriously ill medically or surgically also tend to be more disturbed psychiatrically. Second, the environmental stimuli during the illness form a background for production of various kinds of content. I think this is extremely important. For example, in common usage if one describes a typical alcoholic delirium tremens, one would ordinarily anticipate that the patients would produce evidences of seeing little mice or little men or pink elephants running around the room. Yet, clinical experience teaches us that the quality of the hallucinations is much more in relationship to the life experience of the patient. Combat veterans in the South Pacific would hallucinate Japanese tanks as a very favorite kind of threatening object. In a city, trucks, trains and moving cars tend to form a background for the production of hallucinatory material. Also, because these people are extremely receptive to external stimuli, though they tend to distort them, what is in their immediate hospital setting becomes a focus for hallucinatory experiences. The specific equipment and life experience of the individual usually determine the character of the hallucinatory experience. So one would expect that a young person, an adolescent, in an hallucinatory experience would be preoccupied with the material which is characteristic of this age

group. Such a patient would be preoccupied with problems concerned with authority, and goodness, and sex, while patients in the older age groups would have a different kind of screen upon which they would project their fantasy and delusion.

Mentioning these things briefly, we can move on to the next set of factors, namely, what are the individual factors which determine the kinds of psychotic response? I think it is important to point out that not all individuals who are similarly exposed to known toxic agents show reactions. Also, when the organic reactions do occur in response to the same stimulus, they differ markedly in their characteristics. Some feel that the pre-psychotic personality may give a very good clue as to the kind of psychotic reaction which may appear later. For example, in working with the alcoholic group it has been noted that the pre-psychotic personality of the patient who develops what is called the Korsakoff psychosis is likely to be described as more "outgoing." He has the characteristic personality traits which accompany the telling of tall stories, which the introverted group does not commonly show. Patients who develop alcoholic hallucinosis have a different kind of personality makeup, usually described as schizoid.

Also, an interesting and significant fact is that patients may react in precisely the same kind of way to differing noxious agents. I have in mind a patient who developed a paranoid and confused episode following the administration of relatively small doses of ACTH for lupus erythematosus. She was cleared of the psychosis after the drug was withdrawn. Because of evidence that some drugs of the atabrine group may be beneficial in this disease, she was then started on atabrine. She responded with precisely the same kind of psychotic reactions in terms of content and form that she did with ACTH. This patient makes a good clinical point.

I think it is important to have some kind of neurophysiologic correlation. We can see that those agents which act directly upon the central nervous system may result in a different set of reactions than those which do not act directly.

We may also see another phenomenon—and this has been questioned by some—the so-called release phenomenon, and perhaps this might be illustrated in this way: A patient may be admitted to a hospital with a bromide psychosis. After the excretion of the excessive amounts of bromide, sufficient to return blood levels to normal, the patient may

continue to remain in a chronic psychotic state which is indistinguishable from schizophrenia. What is postulated is that these reactions represent a kind of release phenomenon, taking away inhibitory factors and permitting this other kind of reaction to be manifest when the cortical controls are not so strong. Most of what we see in these reactions is an indication of how completely brain function is disorganized, and the recovery rate is in relation to that portion of the brain which is not severely involved in the pathologic process.

I would like to mention some of the agents which are important in the treatment of neuropsychiatric disturbances and which produce psychotic reactions. For example, morphine, while producing many symptoms of both a psychological and physiological character, rarely produces psychotic reactions. When these psychotic reactions are produced they generally occur in individuals who are considered to have been prepsychotic or actually psychotic before morphine administration, or morphine addiction may have been present.

With the barbiturates the problem is quite different,—two types of psychotic responses are seen: First, in addiction to barbiturates or in large overdoses (often with suicidal intent) one can see the development not only of ataxia, dysarthria, and a clouding of the consciousness, but also the development of hallucinations and delusions. In the abrupt withdrawal of barbiturates, specific symptoms may also develop. However, it is important to note that these symptoms develop only under certain conditions. These are, first of all, that the patient must have been receiving a minimum of 1 to 2½ gm. of barbiturates daily for at least a month. Apparently, in doses less than this the withdrawal symptoms are not seen. Tremors and restlessness develop within eight hours after the last dose of barbiturate, and convulsive seizures are a frequent concomitant of this syndrome. As a matter of fact in one of the series reported from the U. S. Public Health Service Hospital at Lexington, Kentucky, convulsive seizures occurred in 80 per cent of the group from whom barbiturates were abruptly withdrawn. The psychotic picture is also frequently seen following abrupt withdrawal but in somewhat lower incidence than the convulsive seizures, and tends to appear somewhat later in the picture. It may appear usually within four to seven days after the barbiturate has been withdrawn, and tends to disappear spontaneously whether the patient is treated with more barbiturate or not. However, the course is considerably more stormy if barbiturate is not

resupplied to the patient.

The bromide psychosis has been discussed at length previously, and I would only add that in the absence of a positive history and without evidences of a high blood bromide level we are unable to differentiate it, except by minor clues not related to the psychiatric picture, from any other organic toxic psychosis.

I should like to close with brief mention of one group of drugs that have caused a considerable amount of discussion and for good reason, namely, the steroids. These preparations are used in the treatment of the collagen diseases as well as for a host of other diseases. I think it is important to point out what variables are involved and which seem to influence production of psychoses in those who are receiving these drugs. From the standpoint of classification the following psychotic reactions are seen: In our series, organic reactions with a delirium component tend to dominate the entire diagnostic panorama. They form more than half of all of the patients admitted to our hospital with steroid psychosis. We see in lesser percentage, a group of patients who also demonstrate clouding of consciousness, delusions and hallucinations but who also seem to become psychotic on smaller doses than the first group mentioned, and who seem to run a course which is not so directly related to concentration of the dose. These mixed schizophrenic and organic pictures tend to last longer than the two or three weeks that are characteristic of the typical organic psychosis. While giving these drugs, often given to patients who are seriously and critically ill, whose adjustment to life is threatened constantly (not only as it is in most cases by threat of death but also in some few by threat of recovery), we may witness the appearances of acute schizophrenic reactions. We may also see, in a fairly significant proportion, the development of pure mood disorders with pathologic euphoria or with severe depression associated with administration of these drugs. The dosages at which patients may present these reactions are much less predictable than those in the delirium group who develop the organic reactions. We can relate these reactions roughly to dosage, to the underlying disease and its complications, and also, I believe to a lesser extent, to the attitude of the physician. To demonstrate how the physician's enthusiasm may produce these euphoric reactions, I recall a young boy we were asked to see who had rheumatoid arthritis, of not too serious a character, for about five years. He was started on ACTH, by an enthusiastic physician, early in the

course of the experimentation with this medication. This enthusiastic attitude was picked up by the patient. After his first dose of 25 mg. of ACTH the ward staff were much disturbed to see him running down the ward doing hand springs and cart wheels exclaiming how good he felt. They were properly concerned and were also properly concerned with the rebound phenomenon which did occur after the withdrawal of the drug. He became unusually depressed and was then transferred to the psychiatric service for consultation and treatment. This demonstrates the influence of the physician's attitude about the medication as well as the unrealistic hopefulness of the patient, in relation to the resulting psychiatric picture.

I don't think I have to discuss the treatment of the psychoses but perhaps this can be developed during the question period.

MODERATOR REZNIKOFF: Thank you, Dr. Stern. I hope that some of the audience will ask questions about treatment. We have now discussed two phases of this subject. The interesting feature of Dr. Stern's remarks was that very often the emotional reactions of the patient to these drugs really are accentuations, if I understood him correctly, of a person's previous personality. You can't depend on that however. I remember a gentleman who was a perfect husband; used to come home every night, kiss his wife, give her his pay envelope once a week, help wash the dishes, etc. One night, he came home, she put out her lips for a kiss, he smacked her in the jaw and she landed at the other end of the room. The police smelled his breath, and couldn't find any alcohol. It was not until a physician came and took a careful history, that it was found that he was suffering from methyl bromidism. Maybe that was his personality, but he had kept it well in check.

The next speaker, Dr. Wasserman, will talk to us about the hematologic phases of this subject.

DR. LOUIS R. WASSERMAN: The rapid developments in therapy and ready availability of most therapeutic agents have brought about a marked increase in the toxic reactions affecting the hemopoietic system. It is not infrequent for dangerous, even fatal, complications to occur following the injudicious use of some of these agents. Thus these side reactions may constitute a more serious hazard to the patient than the disease for which treatment has been given.

The extent of the toxic reaction affecting the blood or bone marrow appears to bear little or no relationship to the dose administered; unusual

TABLE I

TOXIC RESPONSE OF HEMATOPOIETIC TISSUE
TO THERAPEUTIC AGENTS

I. TYPE RESPONSE
- A. Hypoplastic or Aplastic Anemia
- B. Myelofibrosis
- C. Agranulocytosis
- D. Thrombocytopenia
- E. Hemolytic Anemia
- F. Leukemia?

II. MECHANISM
1. Direct Toxic Action
2. Hypersensitivity
3. Stimulation

side reactions to prior therapeutic trial enhance the probability of a toxic response to a subsequent course of the agent; and only if recognized early may the hypoplastic state be reversible.

Although only a small percentage of the population exposed to these therapeutic agents is affected adversely, nonetheless an appreciation of the possible side reactions and early recognition of them are essential if grave consequences are to be avoided.

The varieties of toxic responses of the hemopoietic system are noted in this slide (Table I). The first four groups have been classified by Osgood under the "Hypoplastic Syndromes" and, together with the drug-induced hemolytic anemia, represent the greatest number of the toxic responses of both the blood and bone marrow. The development of leukemia has been included as a possible result of toxic damage to the marrow because of the circumstantial relationship to benzol derivatives, radium and other radioactive isotopes and the increased incidence in radiologists. To this group one should also add the occurrence of lupus erythematosus cells in (1) hydralazine-treated individuals who manifest simultaneous serum disease symptoms; and (2) in severe allergic states due to penicillin. This L.E. phenomenon probably represents some disturbance in the enzyme systems of the white cells and plasma.

The most common mechanism for these toxic syndromes may be ascribed to the group of hypersensitive reactions. In those cases mani-

festing an explosive onset, within hours, of one of the hypoplastic syndromes, some type of antigen-antibody reaction involving one or more specific cell types in the peripheral blood must be postulated, and in many instances of hemolytic anemia, thrombocytopenia, and agranulocytosis due to drugs, such antibodies have been found. A hypersensitive mechanism has also been thought to act on the bone marrow hematic cells with a maturation arrest of the myeloid elements or megakaryocytes.

In these cases, the drug apparently acts as a haptene forming an antigenic complex with a specific cell protein leading to the formation of an abnormal antibody such as a hemagglutinin or leukagglutinin with a resultant hemolytic anemia or agranulocytosis. The presence of the drug may or may not be required for the action of the antibody on the red and white cells but in the case of platelets with thrombocytopenia the drugs appear to be necessary for the *in vivo* as well as the *in vitro* demonstration of the hypersensitivity reaction.

In those hypoplastic reactions of a more chronic nature which occur only after prolonged use of an agent such as x-ray, the mustards, the antifols and others, the direct toxic inactivation of one or more of the enzyme systems of the marrow cells may be important, but even in those cases occurring after chronic drug exposure such as chloramphenicol, the same hypersensitivity mechanism probably accounts for a large number of the hypoplastic states.

Time does not permit a listing of each and every agent implicated in these hypoplastic syndromes. It is important to understand that few if any of the drugs including antibiotics utilized by us at this time are devoid of occasional to rare toxic manifestations.

Whatever the mechanism for the production of hypoplastic states, whether by direct action on the enzyme systems of these primitive cells or by some hypersensitivity reaction involving a panantibody acting on these marrow elements, it must be due to either an inhibition of cell division or a block in the development of the cells. When primitive cells divide, one cell must remain immature to continue the process of cell division whereas the other divided cell matures and is destined for delivery into the circulation as an erythrocyte or granulocyte. A defect in any of the biological processes controlling this division and maturation of the hematic precursor cells may produce a hypoplastic state.

The findings in aplastic anemia, secondary to some toxic agent, are

similar to those of the idiopathic variety with pancytopenia and an empty marrow. Although it is possible that early in the course of the toxicity there may be a generalized maturation arrest, one is more prone to see hypocellularity with an increased fat content in the marrow. If fibrous tissue proliferation ensues, this usually occurs after a prolonged period of exposure and may actually be an end result of bone marrow aplasia.

A partial list of agents producing agranulocytosis may be seen in this slide. One should note that chlorpromazine has been implicated rather frequently of late in the production of granulocytopenia and that hydralazine will not only produce an agranulocytosis but simultaneously L.E. cells may be found if the slides are examined carefully.

Similar mechanisms, as mentioned previously, are involved in the production of agranulocytosis. In those cases secondary to drug toxicity the hypersensitive reaction appears to be the most common with circulating antibodies against granulocytes demonstrable in the blood in some cases. As in thrombocytopenia, however, there is good evidence that there is a dual action of the hypersensitive reaction. Thus, not only do the leukagglutinins act peripherally with agglutination or lysis of the granulocytes but a marrow effect with a maturation arrest is frequently seen.

The degree of leukopenia is not necessarily an index of the dosage of the drug administered and may range as low as a few hundred white cells.

The appearance of monocytes in the blood indicates recovery and may be taken as a good prognostic sign. This is seen on the left hand slide here. As has been stated before, two types of marrow reaction may occur, that showing hypoplasia of the myeloid elements due to inhibition of cell division, probably the most common marrow response, and that showing a maturation arrest at an early myeloid level. The type of marrow found may also be a function of the time at which the aspiration is performed. Following a period of inhibition of cell division there may be a proliferation of primitive white cells at an early cell level. A marrow showing such a maturation arrest is demonstrated on the right hand side of this slide with the block at the myelocyte level.

This case of agranulocytosis was due to one of the barbiturates with the course depicted in this slide (Fig. 1). The patient was admitted to the hospital for a neurologic complaint, given one capsule of the offend-

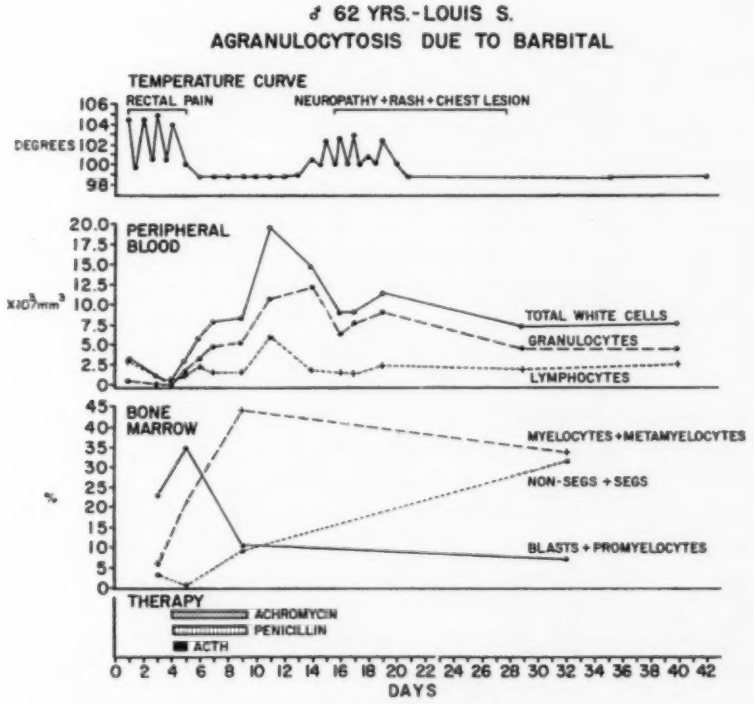



Fig. 1

ing agent for sleep the first night and developed the events shown here with a severe granulocytopenia. Following the leukopenic phase there is frequently a rebound with a leukocytosis as is demonstrated here. Recovery was complete in this patient.

Most of the agents causing thrombocytopenia are to be found in the lists already discussed. It would be difficult to exclude any drug from causing one or more of the hypoplastic syndromes.

The most common mechanism responsible for drug induced thrombocytopenia is again that of hypersensitivity. Ackroyd in studying the mechanism of Sedormid purpura demonstrated the development of platelet agglutinins and lysins which under special conditions could produce thrombocytopenia. These same antibodies presumably also act

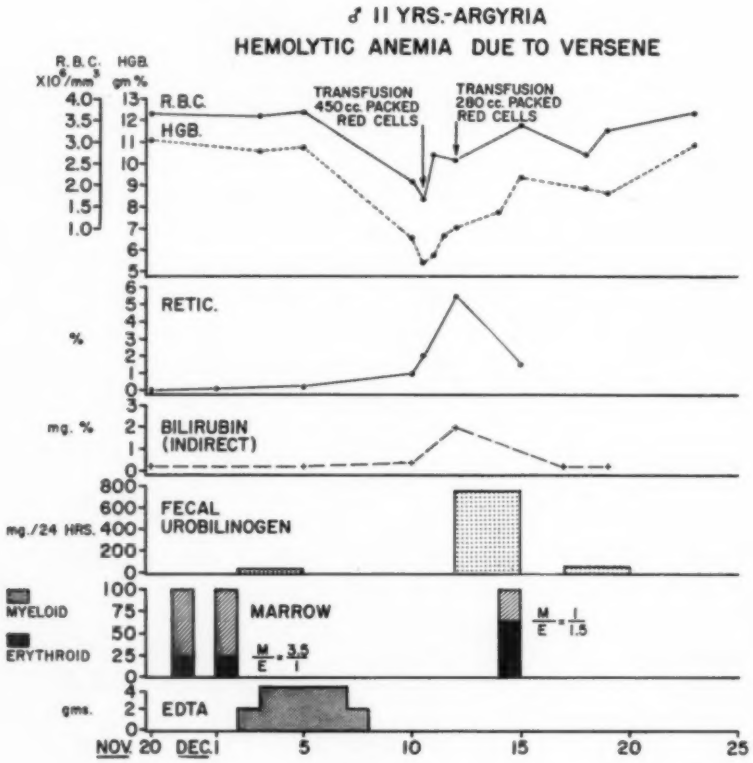



Fig. 2

on the megakaryocytes for one sees a maturation arrest of these platelet precursors as well. It is difficult to ascertain whether a third mechanism for thrombocytopenia, that due to R-E stimulation, is occasionally involved. The rapid disappearance from the peripheral blood of platelets or other cellular elements when antibodies cannot be demonstrated by our most delicate techniques would speak for an increased phagocytosis by the R-E cells of platelets, red cells or white cells presumably sensitized by opsonins or other immune bodies.

The usual blood findings associated with thrombocytopenia are seen in this slide. In the bone marrow one may find a diminution or even absence of megakaryocytes in those cases exposed to the anti-neoplastic

agents or drugs affecting the marrow directly. Where a hypersensitive mechanism exists one frequently finds a maturation arrest of the megakaryoblasts and perhaps an eosinophilia. Since this same picture may be found in thrombocytopenia not drug-induced, the differential diagnosis frequently must rest on a good history.

The characteristic purpuric rash seen in a case of thrombocytopenia, this due to quinidine, is seen in this slide. Although anti-platelet antibodies could not be demonstrated in the serum directly by the usual methods, inhibition of clot retraction by the Ackroyd technique was positive. The only tube containing patient's blood plus quinidine, tube #4, revealed no retraction of the clot with retraction in all the controls.

Hemolytic anemia may be caused by any one of a large number of drugs, a partial list of which is seen in this slide. Amongst the newer agents implicated are Versene, Aureomycin and Benadryl.

An example of Versene-induced hemolytic anemia is seen in this slide (Fig. 2). This 11 year old boy with marked argyria was treated with Versene when it first became available three or four years ago. Fortunately, hemoglobin pigment balance studies were being performed for other reasons, when there occurred a sharp drop in hemoglobin and red cells, a rise in bilirubin and reticulocytes, a change in the myeloid: erythroid ratio in the marrow and a tremendous increase in fecal urobilinogen excretion. With discontinuance of the medication the blood picture reverted to the pre-hemolytic state.

In the next slide are noted the various mechanisms involved in the causation of drug-induced hemolytic anemia. In this syndrome the direct action on the circulating red cells plays a most important role. Since the red cell life span is so long any central marrow effect would not be obvious for many days or weeks. Drugs causing hemolytic anemia produce changes in the stroma as well as the hemoglobin of the erythrocyte with Heinz bodies, fragmented red cells and the abnormal hemoglobins met- and sulf-hemoglobin.

The hypersensitive mechanism is probably again important even though immune antibodies may be difficult to demonstrate. The findings in the peripheral blood may be diagnostic of a drug-induced hemolytic process if Heinz bodies are searched for, and one notes fragmented cells or the peculiar brownish red cells of methemoglobin or sulfhemoglobin blood. The marrow shows an erythroid hyperplasia characteristic of all hemolytic processes.

TABLE II

THERAPY OF DRUG INDUCED BLOOD ABNORMALITIES

1. STOP THERAPEUTIC AGENT
2. FRESH BLOOD TRANSFUSIONS
   a) Collected in plastic bags or silicone-treated bottles
   b) Polycythemic blood
   c) Platelet transfusions
3. ANTIBIOTICS
   a) If platelets are low, avoid intramuscular injections
4. STEROIDS?

One final possible toxic reaction remains to be mentioned. We have been impressed for some time with the occurrence of acute blastic leukemias as an end stage of aplastic anemia induced by drugs, hair dyes, arsenobenzol derivatives and radiation. The cause and effect relationship of the last appears to be better documented than the former agents. Nevertheless it appears to be more than chance that three of our patients dying of blastic leukemia gave a history of long exposure to arsenic compounds. Certainly if cancer can be ascribed to arsenic it does not appear far fetched to suspect the chemical as an etiologic agent in acute leukemia. In two other patients dextro amphetamine had been taken for months preceding the onset of the leukemia. If radiation can induce a greater incidence of leukemia in those radiologists chronically exposed to it, radiometric agents may similarly produce abnormal cell proliferation. We postulate that the toxic agent acting on the bone marrow may produce areas of hypoplasia. The reparative stimuli are altered in some way, producing abnormal fibrous tissue and hematic cell proliferation and perhaps even leukemia. Speculation such as this does not appear to be too remote from the actual occurrences.

The therapy of these toxic manifestations of therapeutic agents is simple but not always successful (Table II). First and foremost the drug must be stopped. Transfusions, if necessary, should be with fresh blood and preferably collected in plastic bags or silicone treated bottles if viable platelets are necessary. We have not had too much success with platelet transfusions but it may well be that with better and easier methods of preparation these platelet transfusions will become more

useful. The introduction of antibiotics has certainly improved the prognosis in these hypoplastic states. Any of the broad-spectrum antibiotics can be used but if thrombopenia is present, injections are best avoided because of the danger of hemorrhage. The case for steroids still is obscure, but where a hemorrhagic tendency exists cortisone or Metacorten should be used.

Where a potent therapeutic agent must be used, an appreciation of the dangers which might occur would call for a careful blood count prior to therapy to be followed by frequent blood examinations as well as a careful appraisal of the physical status for hemorrhagic phenomena, sore throat, fever, arthralgias. Much has already been said and written about the use of potentially dangerous agents for treatment of minor disorders. Certainly the majority of toxic drug reactions would not have occurred if the risk of the disease had been weighed against the dangers of the drug used.

MODERATOR REZNIKOFF: Thank you, Dr. Wasserman.

*I have a few questions, and all directed to Dr. Rose. The first one is this: How does the general practitioner determine whether Monilia infection is the cause of the patient's untoward symptoms of gastrointestinal disturbance, such as diarrhea, etc.?*

DR. ROSE: He obtains a specimen for culture.

MODERATOR REZNIKOFF: *And that is the only way you can tell?*

DR. ROSE: As a matter of fact it can easily be determined merely by examining a stained smear of the feces.

MODERATOR REZNIKOFF: *I suppose if a practitioner is using an antibiotic, and he finds his patient is suddenly complaining of pruritus and diarrhea, he should be sufficiently alert to suspect that the drug may be causing the trouble?*

DR. ROSE: I should imagine so, and I think that most practitioners have the equipment to do a Gram's stain of the material obtained. Instead of finding predominantly gram-negative bacteria they would see large gram-positive organisms which could hardly be mistaken.

MODERATOR REZNIKOFF: *The next two questions are really the same. Can the gastroenterocolitis following the use of tetracyclines be ameliorated by the combined use of anti-fungal remedies (mycostatin)? And part of another question a good deal like it: Dr. Rose, does the addition of mycostatin to the antibiotic prevent the gastrointestinal disturbances that may follow the use of the antibiotics alone?*

DR. ROSE: I am sorry that I cannot answer the question. I have no information on the point.

MODERATOR REZNIKOFF: *Does anybody know? Dr. Wasserman!*

DR. WASSERMAN: No.

MODERATOR REZNIKOFF: *Dr. Stern!*

DR. STERN: No.

MODERATOR REZNIKOFF: My own experience is that we begin to use mycostatin after the apparent fungal infection arises, usually in the mouth. I have had no experience with its use in gastrointestinal conditions.

*Does anybody in the audience wish to answer that question?* (There was no response.)

*Dr. Stern, I think this is directed to you: Kindly discuss in a little more detail the neurotoxic effects of streptomycin and dihydrostreptomycin.*

DR. STERN: I think Dr. Rose mentioned it previously. Eighth nerve involvement is our chief concern. It is reported that the vestibular part of the eighth nerve is involved perhaps a little more frequently than the acoustic in dihydrostreptomycin therapy, while the hearing part is said to be more commonly involved in streptomycin therapy. I imagine that is the chief complication to be concerned with.

MODERATOR REZNIKOFF: *I shall ask Dr. Wasserman the next question: You include Phenergan among the antihistaminics capable of inducing agranulocytosis. Can you give us a reference in the literature offering evidence confirming such a claim?*

DR. WASSERMAN: Oh, yes. All these references were taken from well documented cases.

MODERATOR REZNIKOFF: I believe that is in a review by Osgood in 1953 in the *J.A.M.A.* and also in the *Annals of Internal Medicine*. Recently two articles, one by Vaughan and another by Stohlman in the *New York State Journal of Medicine* reviewed many of the drugs.

DR. WASSERMAN: This is from a list I received from a subcommittee of the American Medical Association listing all of the agents that had been implicated as causing hemopoietic disturbances. That drug was on the list.

MODERATOR REZNIKOFF: When I was in Argentina a few years ago doctors there told me that they never saw a case of aplastic anemia following chloramphenicol, and they used it constantly in large doses over

a long period of time for typhoid fever and other diseases. So you can see how people differ in their experiences.

*Dr. Rose, a question was asked: Can digitalis produce a skin itch?*

DR. ROSE: I am not familiar with it. It may occur.

MODERATOR REZNIKOFF: I would like to call your attention to the fact that patients are being given medications for some disorder, and it is sometimes a little difficult to determine whether the disease is not responsible for the toxic effect rather than the drug. However, I am not aware that digitalis commonly produces pruritus.

*Another question: Is there any danger that Diamox may produce hepatic coma or disorientation in hepatic fibrosis of congestive failure? It goes on: These are reported in Laennec's cirrhosis after Diamox. How do mercurial diuretics compare in this respect? First of all we have a question whether Diamox may produce hepatic coma or disorientation in hepatic fibrosis. Are any of you gentlemen acquainted with that?*

DR. ROSE: I am afraid my experience is not sufficiently extensive to permit me to answer the question, Dr. Reznikoff.

MODERATOR REZNIKOFF: One effect of Diamox that I know has been reported is acute neutropenia or agranulocytosis. I am not aware of any of these other conditions occurring.

DR. ROSE: I am not entirely certain in what context the question concerning mercurial diuretics is asked.

MODERATOR REZNIKOFF: *I think that the question is this: Here is a patient who apparently has cirrhosis of the liver probably secondary to congestive heart failure. I presume the patient has edema and either Diamox or the mercurials are used for the edema. Am I corrct? Is this the interpretation of the question?*

DOCTOR: That is right.

MODERATOR REZNIKOFF: *Then this gentleman wants to know if as a result of the use of Diamox or mercurial diuretics hepatic coma or some disorientation might occur?*

DR. ROSE: I certainly can answer the question with respect to mercurial diuretics. If these drugs provoke a good diuresis in an individual whose liver function is border line, so to speak, and if the patient is thereby over-dehydrated and the blood volume is reduced beyond a certain point, he may go into shock and ultimately display what is commonly called hepatic coma. I presume that if this can occur with the mercurial diuretics—and we know it does—that the same thing might

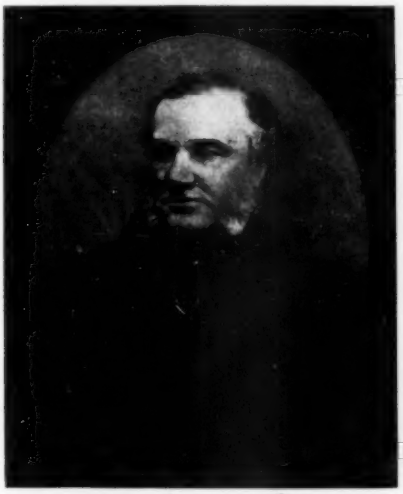
happen following Diamox, but what the comparison between the two drugs might be I do not know.

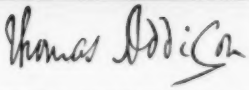
MODERATOR REZNIKOFF: In the old days when a patient had uremia and marked edema we used to treat him with hot packs, and we wondered why the patient had convulsions. Well, we assumed we got rid of the fluid but in accomplishing that, the toxic agents involved became more concentrated.

*Are there any other questions from the floor?*

If not, I should like to make a few statements by way of summary. This is a rather important subject not only to the patient but also to the doctor in several ways. Many doctors are being sued these days for accidents that occur, and they would like to know how they can prevent them. Unfortunately, we can't always prevent these accidents by sequential blood counts. We have all had the experience of having a patient who, early in the day has a normal blood count and that night develops acute agranulocytosis. Nor can we select our patients and determine who would be sensitive to what. There is no way of determining in advance who will respond in a bad way to a therapeutic agent. There are no animal experiments that can be used to determine what these agents will do. We know all patients will eventually show the depressing effects of urethane, Myleran, 6-mercaptopurine and radiation. We also know, however, that many patients will take many of these drugs that have been mentioned and shown on the screen without any untoward effect, and some will even have bad effects with a single or a few doses of aspirin. So the physician ought to use drugs when they are indicated and under no other conditions. He ought not to use drugs that might be toxic when he can use simple remedies; and after all is said and done he wants to be lucky!

I wish to thank the members of the Panel for their presentations and discussion and the audience for its interest and attention.





THOMAS ADDISON, 1792 — 1860

# THE CENTENARY OF ADDISON'S DISEASE*

S. ZELIG SORKIN

IN 1860, five years after Addison's publication,[1] George Harley,† in discussing a case before the London Medical-Chirurgical Society, presented the new German views against the possibility of the existence of Addison's disease. To this Addison replied, "In this case I foretold that there would be found at these two little spots on the body two lumps of disease, and this turned out to be true. Will Dr. Harley tell me what are the probabilities that this was chance as he maintains?" Thus we see that despite Addison's conviction in the correctness of

* Presented before the Section on Historical and Cultural Medicine of The New York Academy of Medicine, May 9, 1956.

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† Cf. letter of Samuel Wilks; Rolleston[2] p. 340.

his discovery, others were articulate in their scepticism. This is easily understood when it is recalled that virtually nothing was known, at the time, of the function of the adrenals.

Addison described his treatise "On the Constitutional and Local Effects of the Suprarenal Capsules," published in 1855, as a "first and feeble step towards inquiry into the functions and influence of these organs." This was truly a "first step" in that direction, but a step that was far from feeble. His monograph provided the first evidence that the suprarenal glands are essential to life. Addison's remarkable description of the disease which bears his name has proved to be so accurate and complete that to this very day most cases can be diagnosed without further aid if one recalls the cardinal symptoms in the author's words: "general languor and debility," "remarkable feebleness of the heart's action," "irritability of the stomach," "wasting without cachexia" and "a peculiar change of color in the skin."

Addison's achievement was even more than that of a classic description of disease. His contribution, Claude Bernard's[3] promulgation of the conception of internal secretion and Brown-Séquard's[4] experimental demonstration of the vital nature of the adrenals, all within the same year—1855, combined to set the initial peak in the development of endocrinology.

In the three centuries between the first description of the adrenals by Eustachius, in 1563, and Addison's discovery, considerable knowledge[5] had accumulated concerning the anatomy, histology and, to a lesser extent, the morbid anatomy of the adrenals; but no definite knowledge of their function had emerged. A spurious central cavity described by Schenk in 1600 was corroborated by Bauhin in 1606, who found a black fluid in the cavity. In keeping with the medical concepts of the time, Casper Bartholin recognized the fluid as black bile, "atrabilia," and thereby helped to establish a misconception which persisted almost until the mid-19th century. Casper Bartholin, and his son Thomas who misnamed the glands "capsulae atrabiliarae," believed that the capsules purified the black bile in some way to permit its passage through the kidneys. Others believed that the suprarenals functioned only in fetal life or early childhood, that they took the place of the kidneys in the fetus, or that they produced the meconium. Anatomical studies had led to the recognition of the adrenal as a ductless gland or *Blutgefaessdruese* like the thyroid, thymus and spleen, and like them

was thought to have an internal secretion. By 1855, many morbid anatomical data had been gathered, but it was doubted that the adrenal bodies could be the seat of a significant primary affection. No one had attempted to correlate morbid change in the glands with clinical symptoms.* On the contrary, it was held that disease of this organ was not amenable to clinical diagnosis and further, that morbid changes in the glands cast no light on their function.

Viewed against this background, Addison's delineation of a definite clinical entity arising from disease of these glands was an outstandingly original contribution. It prompted Samuel Wilks[6] to suggest that Addison be counted among the exceptional few in history who have possessed knowledge in anticipation of their time. Wilks' appraisal finds corroboration in the fact that there was no significant advance in knowledge of the adrenal from that time until the discovery of epinephrine, 40 years later. However, Addison's achievement also fits in many ways into the context of its contemporary medical history. The description of Addison's disease represents a high point in the development of the correlation of morbid anatomical change with clinical observation, less in the sense of knowledge compiled than of conceptions and methods developed. Morgagni's influence is readily apparent. Consider in this connection Klemperer's[7] statement that "By correlating the fleeting manifestations of disease, as seen in the living, with the tangible organ alterations in the dead body, Morgagni established the first scientific system in medicine," some 75 years earlier, and "provided the foundation for diagnostic medicine as it developed in the 19th century." Even earlier, Sydenham had emphasized the distinction between the patient and the illness by stressing the objective quality of the illness in terms of pathological symptoms rather than the patient's humors. This served as a means for delineating specific diseases based on symptomatology, a nosological method which depended upon, and thus emphasized, clinical observation as exemplified by Addison's work. Addison's way was also paved by Bichat's demonstration early in the 19th century that diseases were actually located in the tissues of the organs, an extension of Morgagni's organ pathology, and by Auenbrugger and Laennec's

* Richard Bright might have anticipated Addison by 25 years. "Case CXIX" of his "Reports of Medical Cases" (London, 1831, vol. 2, p. 247) is entitled "Serous effusion under the arachnoid and into the ventricles in a case of emaciation with bilious vomiting and diseased renal capsules." Bright noted the patient's very dark complexion and placed the adrenals, described as showing "scrofulous suppuration," in the pathological museum. However, he failed to correlate the clinical manifestations with the adrenal pathology, a circumstance which prompted Wilks[6] to suggest that Bright "did not perceive the true value of his own observations."

invention of percussion and auscultation as methods of physical examination. Bichat's work provided another step toward localized pathology permitting the development of a nosology based on a correlation of symptoms observed at the bedside with localized morbid change. The newer techniques of clinical examination of Auenbrugger and Laennec favored more thorough observation of the patient and led to a profound change in clinical medicine. As Shryock[8] states, "Thereafter physicians would not simply observe their patients—they would examine them." The correlation of pathological changes with the now more complete and more valuable clinical findings led to the abandonment of nosologies based merely on symptoms. Clinicians began to picture the pathological changes that occurred in living patients. The conception of localized pathology received acceptance more generally and the older humoral theories were being further discarded.

Social and economic evolution between 1750 and 1850 exerted a marked influence on the development of medicine.[8] The development of commerce and the early industrial revolution led to rapid urbanization. The crowded cities and the slums which arose brought a soon to be fulfilled need for the development of hospitals. Crowded city life contributed to an increase in the incidence of pulmonary and other organ (including adrenal) tuberculosis.

Guy's Hospital, an outstanding example of the "hospital movement" just mentioned, was almost a century old when Addison went there to study in 1817. However, it was during the second and third quarters of the 19th century that Guy's became world famous. In this development Addison exerted an influence equal to or greater than that of Guy's other great men. The younger son of a grocer, Addison was a well-trained physician when he entered Guy's Hospital as a student. Intended by his father for the law, he had received a sound classical education at the Newcastle Grammar School and in 1815, at the age of 22, he received his medical degree in Edinburgh. In that year he came to London to practice, but first obtained the appointment of house surgeon to the Locke Hospital where emphasis was placed on the treatment of syphilis. He then entered practice and joined the Public Dispensary where he became extremely expert in dermatology. In 1818, he enrolled at Guy's as a "perpetual physician's pupil," and in 1824 was appointed assistant physician. Then, despite the influence possessed by competitors for the position, one of whom came recommended by the King, Addison

was appointed lecturer in materia medica, in which he earned his first reputation as a popular instructor. William Hale-White tells us, "He even made the dry bones of materia medica attractive." Throughout the entire period of Guy's growth to fame, Addison was its foremost clinical teacher, exerting a profound influence on all of the Guy's pupils over a period of almost 40 years.

Addison was appointed full physician and joint lecturer in medicine with Dr. Richard Bright in 1873. In the latter year and in 1840 his notable essays on the anatomy of the lung and pneumonia appeared, bearing evidence of the thoroughness with which Addison studied a subject which gained his interest. Other publications[9] reflect his wide interest in and knowledge of clinical medicine as well as his originality. Of special interest is his paper "Observations on Fatty Degeneration of the Liver," published in 1838. This paper illustrates how early his interest in anemia began, an interest which was to culminate in his description of "Idiopathic [pernicious] Anemia" and of "Melasma Suprarenale," 17 years later.

Addison's monograph on "The Constitutional and Local Effects of the Suprarenal Capsules", published in 1855, is truly a remarkable publication. It is probably the only paper which contains an original description of two diseases, both of which have been named for the author. Addison's modest preface did not conceal the fact that he was convinced he was rendering original descriptions of two diseases. An earlier paper, "On Anemia: Disease of the Suprarenal Capsules,"[10] read on March 15, 1849, is considered by some to be the first account of pernicious anemia. However, in that paper he stressed the fact that the three cases autopsied all showed the adrenals to be diseased, and in two of the cases the adrenal changes were the only lesions in the body. He very probably erred at that time in considering disease of the suprarenals an etiological factor in the anemia, but in 1855 he described "Idiopathic Anemia" and "Melasma Suprarenale" as two independent clinical entities. The "Idiopathic Anemia" was characterized pathologically by the absence of any striking morbid change, whereas easily discernible suprarenal disease was held responsible for "Melasma Suprarenale."

The 1855 monograph states clearly that Addison's interest in idiopathic anemia led to his discovery of the disease associated with extensive suprarenal destruction. He wrote, "It was whilst seeking in vain to throw some additional light upon this form of anemia that I stumbled upon the

curious facts which it is my more immediate object to make known to the profession." His interest in anemia may be traced to his earlier attempts in 1838 to associate fatty degeneration of the liver with a "bloodless, almost semitransparent and waxy appearance of the skin." In his description of "a remarkable form of anemia" in 1849 he wrote, "The whole surface bears some relation to a bad wax figure." Thus Addison's interest in the patient's appearance in anemia and in fatty degeneration of the liver, a common finding in pernicious anemia, appears to have led to his description of "Idiopathic Anemia" which then led to the discovery of "Melasma Suprarenale." Whether or not the discovery of Addison's disease can be traced in this fashion, similar consideration led Wilks to state, "This discovery has been spoken of as a kind of guess or due to some peculiar inspiration with which Addison was endowed; but so far from either of these suggestions being true, his memoir on the subject was the result of years of observation and painstaking."

We should not disregard Addison's statement that he "stumbled" on the facts which led to his major discovery. This implication is supported by the circumstance that Addison left some points unclear; points he might easily have clarified. The diseased condition of the adrenals which he reported in the three cases of the "remarkable form of anemia" in 1849 was not then nor subsequently described. Addison also failed to mention how his attention was first directed to the pigmentation which he considered "the distinctive mark" of the adrenal disease. It seems not unlikely that, had he started out to seek an explanation of the pigmentation and found it to be disease of the suprarenals, he would have so stated. Gull, who in 1851 recorded the second case in Addison's original series, wrote, "But what condition in the system is it which favors the production of black pigment? Is it some affection of the liver; or is it, as Dr. Addison supposes, disease of the suprarenal capsules?" Since Addison had previously personally observed only a single case of "bronzed skin," one is inclined to credit his use of the word "stumbled." The "disease" or morbid change which he erroneously believed was present in the suprarenals in "Idiopathic Anemia" in 1849, led him to look for clinical manifestations in association with suprarenal disease. Then, through his superior abilities, best described in the words of Wilks as "possessing unusually vigorous perceptive powers, being shrewd and sagacious beyond the average of men," Addison discovered the disease which now

bears his name.

Addison's monograph had one defect. In his enthusiasm to demonstrate the association of skin pigmentation with adrenal disease he added to the six clinically carefully observed and apparently genuine cases five others which were probably not true examples of the disease. As Wilks* wrote, "he went too far and spoiled his treatise by intruding 'spotted' man, a case of malignant disease of the capsule."

Addison's was a lifetime devoted to teaching, hospital work and research. As Hale-White[11] remarked, "He was always at work, either in the wards or in the dead-house," and Wilks and Daldy[9] wrote, "His conclusions were deduced from the most accurate necroscopic inquiries pursued, not only at the well directed postmortem examinations of Guy's Hospital, but at his own residence also, with an assiduousness and sedulous perseverance comparable to the zeal of a Harvey or a Hunter. . . ."

Despite his hospital and teaching position, and the industry he devoted to it, Addison also engaged in private practice. However, he did not have a large practice and was almost unknown to the general public even though he enjoyed an excellent reputation among the profession as a most accurate diagnostician. Munk[12] states that Addison did not "seem solicitous of a large private practice and its coincident emoluments, indeed he was by nature and manners unfitted for it."

Addison appears to have been a self-sufficient and rather aloof person who mixed but little with other men. He did not marry until the age of 54. His wife was a widow, the mother of two children; he had no children of his own. Addison admitted to a highly nervous temperament. He said, "I never rose to address the Guy's Junior [student] Physical Society without feeling nervous." However, his contemporaries were not aware of this shortcoming because of his manner which made him appear not only self-contained, but apparently "domineering and difficult to approach." Throughout his life he was given to bouts of severe melancholy. Wilks tells us "that it was only to some of his nearest friends that he disclosed some of the secrets of his life, his awful fits of despondency associated with some fearsome circumstances which made him wonder that he was still alive to tell the tale."

Addison's mental difficulties became so pronounced in the early part of 1860 that he was compelled to retire from hospital and private

* Cf. Rolleston[9] p. 340.

practice. He wrote,* in reply to a letter of condolence from the pupils of the hospital on his retirement, "A considerable break-down in my health has scared me from the anxieties, responsibilities and excitement of the profession; whether temporarily or permanently cannot yet be determined. . . ." However, when a deputation begged him to reconsider his resignation, he replied, "My work is over, I have left it for others." Rolleston states Addison "Believed that his younger colleagues [mentioning Gull] wished to deprive him of his position; he became suicidal, and though kindly reticence drew a veil over his death, evaded two of his attendants and threw himself out of a window on June 29, 1860."

Addison's paper had immediate and far-reaching influence on the study of the disease and the adrenal glands. Many cases with clinical descriptions and autopsy findings were reported promptly in England. In 1856, in France, Lasègue[13] reviewed Addison's essay, and Trousseau[14] promptly named the disease "Maladie d'Addison." In the same year Isaac Taylor[15] of New York corroborated the existence of the disease by a description of cases with autopsy findings in two instances.

Experimental investigation of adrenal physiology was started promptly after Addison's publication appeared. Brown-Séquard's reports on the fatal outcome following adrenalectomy appeared in 1856. This served to further the interest which Addison had stimulated in the adrenal glands. However, doubt arose concerning their vital properties. Brown-Séquard's results were questioned and satisfactory answers were not forthcoming.

The initial impetus to investigate adrenal physiology was soon spent, probably because Addison's discovery was in advance of the development of methods to perform and study the effects of adrenalectomy.

The initial peak in the development of endocrinology raised in 1855 by Addison, Claude Bernard and Brown-Séquard remained solitary until replacement therapy was initiated, almost 40 years later. When one recalls that the use of body substances as therapeutic measures is very ancient, it is difficult to understand why animal adrenal glands were not employed sooner in the treatment of Addison's disease. This step had to await the development in endocrine disease of the concept of replacement therapy, a logical extension of Claude Bernard's concept of internal secretion. Addison's discovery and Brown-Séquard's experimental confirmation were followed by the extirpation of the thyroid with fatal

* Cf. Wilks and Daldy,[9] p. XVI.

results by Schiff in 1856-8. This work was forgotten until 1884 when Schiff,[16] stimulated by the reports of Reverdin and Kocher of a postoperative hypothyroid state, repeated his experiments and showed that the fatal outcome following thyroidectomy could be prevented by intra-abdominal transplantation of the extirpated thyroid. Felix Semon[17] recognized that the long known cretinism in children, the adult cretinoid disease of Gull (1873) or the myxedema of Ord (1877) and the postoperative hypothyroid state were all due to inadequate thyroid secretion. This was proved experimentally in 1885 by Horsley, who then made the logical suggestion[18] in 1890 that substitution therapy be attempted by grafting an animal's thyroid into a myxedematous patient. This proved successful in the hands of Bettencourt and Serrano.[19] The beneficial effect was transitory because the engrafted glands were soon absorbed, but the principle of replacement therapy had been established. Successful results were obtained in the treatment of myxedema by G. R. Murray[20] in 1891 with the hypodermic injection of thyroid juice, and in 1892 with the peroral administration of thyroid extract. Reports[21] of the use of adrenal extracts in Addison's disease began to appear in 1892. However, the results with early extracts were hardly good; it was not until the 1930's that potent cortical extracts were available.

In 1895, Oliver and Schaefer[22] discovered a highly potent substance in adrenal extracts, derived from the medulla of the gland. Abel[23] named the substance epinephrine and promptly initiated its isolation. The hormone was isolated in crystalline form in 1901 by Takamine[24] and independently by Aldrich.[25] Takamine named it adrenalin, and in 1904 Stolz[26] prepared the hormone synthetically. This great achievement unfortunately retarded the development of Addisonian therapy by diverting attention from the adrenal cortex to the medulla. The powerful epinephrine seemed to be exactly what the Addisonian patient needed to overcome his asthenia and hypotension and until the mid-1930's it was used widely, often in conjunction with whole gland extracts.

Fortunately, the importance of the adrenal cortex was not overlooked. Hansemann[27] in 1896, and Karakascheff[28] in 1904, and later others reported post mortem evidence to prove that Addison's disease was due solely to destruction of the adrenal cortex. Significant experimental evidence of the vital role of the cortex was advanced early in the 1900's when Biedl[29] showed that elasmobranch fishes, species in which cortex and medulla are separated, invariably died when the

cortical body was removed, even though the medullary body was left intact. Biedl and others reported that rabbits and dogs would survive removal of all but one-eighth of both glands, providing the remaining portion consisted of cortex. The studies of Stewart and Rogoff emphasized the vital nature of the cortex and demonstrated that neither the adrenal medulla nor epinephrine was indispensable to life or health in animals. In 1927, these authors[30] reported significant prolongation of life in adrenalectomized dogs by administering saline and glycerine extracts of canine adrenal glands. Almost at the same time Hartman[31] and his co-workers, and soon Pfiffner and Swingle,[32] succeeded in prolonging the post-adrenalectomy survival period in animals by treatment with extracts which they had prepared. Shortly afterward, both groups developed cortical extracts capable of maintaining adrenalectomized animals almost indefinitely and of producing dramatic results[33] in the treatment of Addisonian crisis.

The development of a potent cortical extract provided more than an important therapeutic agent. It supplied the impetus and the means for much of the progress attained during the past 25 years in the treatment of Addison's disease and in the advancement of knowledge of adrenal physiology. The ground was prepared for the isolation and synthesis of the individual adrenal cortical hormones. But before this took place, the use of sodium salts was established in the treatment of human adrenocortical insufficiency, a development historically independent of the development of cortical extracts.

In 1932, Robert Loeb[34] made a signal contribution when he recognized that the serum sodium and chloride concentrations were decreased in Addison's disease and demonstrated that the administration of common salt brought about striking improvement in severely ill Addisonian patients by restoring the blood electrolyte pattern toward normal. This contribution provided an essential form of therapy for Addison's disease and disclosed, for the first time, the specific, vital function of the adrenal gland in regulating salt metabolism. Four centuries earlier, Paracelsus, in his treatise, "On Salt and Its Nature," stated dogmatically but clearly, "man can in no wise live without salt." In 1805, De Saussure* demonstrated that minerals were essential to plants and Liebig[35] later extended this demonstration to animals. The contributions during the 19th century of Berzelius, Carl Schmidt, Pfeffer, van't Hoff and Arrhenius,

* Cf. Liebig, J.[35] p. 64.

Salkowski, Sidney Ringer and Jacques Loeb resulted in a marked advance in knowledge of the biological and physiological significance of the minerals and stimulated study of their role in disease. Concerning his discovery, Robert Loeb, son of Jacques Loeb, has written[36] that his interest "in problems of adrenal physiology developed as a by-product of a long series of studies in electrolyte and water metabolism in normal individuals and in certain morbid states, and was not initiated by a particular interest in the endocrine field." In 1932, impressed by a clinical similarity in conditions associated with loss of alkali from the body, he "studied in detail the electrolyte structure of the blood in Addison's disease" and found the changes he sought.

During a period of eight years prior to Robert Loeb's contribution, other authors[37, 38] with a more primary interest in endocrinology reported observations in animal experimental work and in Addison's disease indicating a relationship of sodium salts to the adrenal gland. However, they attributed the beneficial effects of salt infusions in the hypoadrenal state not to correction of a salt deficiency but rather to a washing out of toxins. This inclination to invoke a detoxifying action to explain endocrine function has recurred several times since 1855, suggesting that the "purifying" notions of the old humoralists* had not, as late as 1930, given way completely to the concept of internal secretion. In any event, the significance of the biochemical aberration and consequently of the therapeutic implications underlying the use of sodium in adrenocortical insufficiency was not appreciated until Robert Loeb called attention to the existence of this specific relationship in 1932. Loeb, Atchley, Benedict and Leland[40] and Harrop, Soffer, Ellsworth and Trescher,[41] in their fundamental physiological studies soon disclosed the mechanism of sodium loss via the kidneys in adrenalectomized animals. Recognition of the adrenal-sodium relationship established the blood sodium determination as the first and probably the most accurate biochemical test for the diagnosis of Addison's disease. This test was markedly enhanced in its value when Harrop, Weinstein, Soffer and Trescher[42] promptly demonstrated that sodium deprivation produced hyponatremia in Addisonian patients but not in normal individuals.

Recognition of the adrenal electrolyte relationship was of manifold

* Cf. Thannhauser[39] for a closer relationship of the Galenic humoral pathology to modern concepts of metabolic diseases.

significance, but for the patient with Addison's disease it had the singular and immediate importance of providing the first practical maintenance measure. Synthetic hormones for this purpose were soon to be added, substances capable of regulating electrolyte and organic metabolism, but common salt has retained its place in the treatment of Addison's disease.

The steroid, in many ways the most bountiful, phase of Addisonian therapy is a direct outcome of the search for "the" hormone responsible for the physiologic effect of potent adrenocortical extracts. Initiated in 1930, shortly after the extracts were first prepared, the steroid phase has provided a series of outstanding achievements. The brilliant and exhaustive chemical research of three groups of investigators, headed respectively by Kendall,[43] Wintersteiner and Pfiffner,[44] and Reichstein[45] bore fruit as early as 1934, and soon led to the isolation of 28 crystalline adrenocortical hormone fractions. Including electrocortin or aldosterone, the seven cortical compounds known to possess biologic activity have all been synthesized. This very notable achievement in biochemistry found a counterpart in the unique circumstance that, in addition to their use in the treatment of the relatively few patients with Addison's disease, adrenocortical steroids proved highly valuable in the treatment of a large variety of disorders which appear to have no direct relationship to the adrenal gland.

A very important early development was the partial synthesis of desoxycorticosterone from stigmasterole by Reichstein and Steiger[46] in 1937. Although this steroid, whose occurrence as a natural hormone was very doubtful until recently, is probably not present in the blood in high enough concentration to exert any significant biologic action, it has played a very important role in the history of the adrenal. Because of its potent influence on sodium retention,[47] it has served as the most important hormonal maintenance measure in the treatment of Addison's disease from 1936 until the present.[48-50]

It was soon evident, however, that desoxycorticosterone did not provide complete adrenocortical replacement. The synthetic steroid proved to be without direct effect on organic metabolism and it did not correct the faulty water diuresis noted in 1925 by Rowntree[51] in Addison's disease and used as the basis of the water-loading test of Robinson, Power and Kepler,[52] described in 1941.

That the adrenals were involved in organic metabolism was suggested

as early as 1910 by Porges and Malloizel and Bierry. Porges recorded the first clinical observation of hypoglycemia when he reported its occurrence in Addison's disease. Britton and Silvette,[53] in a series of papers published between 1931 and 1936, reported that adrenalectomy was followed by a disturbance in carbohydrate metabolism manifested by hypoglycemia and a depletion of hepatic and muscle glycogen, changes which could be prevented or corrected by the parenteral administration of adrenocortical extracts. These authors also adduced the first experimental evidence to suggest that cortical hormones influenced renal excretion of water and attributed this to a diuretic action antagonistic to the water retaining effect of the posterior pituitary hormone.[54] In 1940, Long, Katzin and Fry[55] demonstrated unequivocally that the adrenal cortex participated directly in carbohydrate and probably also in protein metabolism. Desoxycorticosterone had only a feeble effect. In the same year Thorn, Koepf, Lewis and Olsen[56] presented evidence of a direct action of adrenal cortical hormone other than desoxycorticosterone on carbohydrate metabolism in man. Eversole, Gaunt and Kendall in 1942 reported the greater efficacy of Compound E in maintaining water diuresis. The sustaining and stimulating interest of Gaunt, Birnie and Eversole[57] in this complex phase of adrenal function has added considerably to its knowledge. In 1949, Thorn demonstrated that the Kepler water-loading test could be restored to normal in Addison's disease with the use of Compound E, which in the interim had become known as cortisone. More recently, based on these facts, the diagnosis of this disease has been facilitated by the simplified water-loading tests of Soffer and Gabrilove[58] and Oleesky.[59] At this point discussion is in order, but time does not permit more than mention by name of the very valuable methods of measuring human adrenocortical function—the eosinophile and the 17-keto-steroid excretion tests—developed by Thorn.[60]

As with the other endocrines, much has been learned concerning adrenocortical function from study of disease in which increased hormone secretion occurs. For our purposes this evening, suffice it for me to say that existence of an adrenocortical organic-metabolism relationship was also evident from observations in Cushing's syndrome, the morbid state described so aptly by Knowlton[61] as "spontaneous hyperadrenalism" in a comprehensive paper on that subject presented before this Academy at a recent Graduate Fortnight meeting.

Demonstration of the adrenals' role in organic metabolism and recognition that this function was exercised by 11-oxy-corticosteroids, and not by desoxycorticosterone, helped to convert the search for "the" cortical hormone into concerted efforts to produce synthetically *all* of the physiologically active fractions in large quantities. Following the demonstration of their steroidal nature, elucidation of the chemical structure was facilitated by the circumstance that fundamental research on the chemical structure of cholesterol, the bile acids and sex hormones had come to fruition between 1932 and 1934, with the establishment of the cyclo-pentenophenanthrene formula.[62, 63] By 1940, the chemical structure of almost all the adrenal steroids had been determined, but it was recognized that despite the presence of steroids in all forms of life, those occurring in the adrenals are not found anywhere else. Thus there remained the exceedingly difficult task of preparing these substances from starting material more bountiful than adrenal cortex.

By the early 1940's, Lardon and Reichstein[64] and Turner and associates,[65] and their respective co-workers, had succeeded in synthesizing 11-dehydrocorticosterone, Compound A of Kendall, and in 1946 Sarett[66] accomplished the synthesis of cortisone from desoxycholic acid. The spectacular results obtained by Hench, Kendall, Slocumb and Polley[67] with the use of cortisone in the amelioration of the symptoms of rheumatoid arthritis and the resultant widespread use of this steroid in other diseases lead to improvement in methods of producing the hormone in large quantities and also to the synthesis of hydrocortisone and more recently to the substituted analogs of these hormones.

The impact of this accomplishment has been so profound, its potentialities so manifold and so far-reaching, that it must remain for the future to determine its full magnitude. The vast sphere of influence of these hormones in the body and the almost infinite avenues of investigation which their availability has opened may be appreciated from the fact that they modify the metabolism of carbohydrate, protein and fat as well as that of sodium, potassium, calcium and water. Their great value as therapeutic agents, common knowledge to the laity as well as to the medical profession, is apparent from the large number of maladies in which they play a beneficial role, varying from that of the relief of pain and other disabling symptoms to the prevention of a fatal outcome. It was almost inevitable that the use of such potent hormones would produce undesirable side effects and present problems requiring skill

and judgment in their clinical use. However, the introduction recently of the halogenated hormone analogs is evidence that the chemists are continuing with undiminished effort to produce synthetic steroids of greater potency and yet having more isolated effects.

The most recent major accomplishment, the total synthesis of racemic aldosterone, was reported[68] in the past few months. The discovery of this hormone may be traced[69] to the potent non-crystalline residue of adrenal cortical extracts obtained in the 1930's by Wintersteiner and Kendall and their respective co-workers. The "amorphous fraction" of Kendall was known from that time to be more potent and to possess wider biologic activity than desoxycorticosterone. However, the excellent results obtained with the potent sodium retaining synthetic steroid in Addisonian patients favored the concentration of efforts on the hormones influencing organic metabolism and diverted interest from further study of the amorphous fraction until recently.

In 1952, Simpson, Tait and co-workers with the use of new methods, reaffirmed the previous knowledge of the potency of the amorphous fraction and also showed adrenal venous blood to possess similar mineralo-corticoid activity. The combined efforts of these workers in London with groups in Basel headed by Wettstein and Neher and von Euw and Reichstein[70] led, in 1953, to the isolation and crystallization of the remarkably potent aldosterone, soon found to exhibit about 30 times the salt retaining activity of desoxycorticosterone. The new hormone appears to have considerably less effect on carbohydrate metabolism than cortisone or corticosterone but many times that of desoxycorticosterone. As with the amorphous fraction, only 1-2 micrograms of the crystalline hormone per kilogram per day suffice to maintain life and electrolyte balance in adrenalectomized dogs. Thus the main hormone regulating sodium, potassium and chloride metabolism has been isolated, crystallized and synthesized, and knowledge of the chemical nature of the adrenocortical hormones probably has been completed.

The Centenary of Addison's Disease comes at the end of a century which has seen the greatest and most rapid progress in medicine. In keeping with this, and despite the fact that this disease was described more than half a century before the vital nature of the adrenal cortex was recognized and 75 years before specific substitution therapy was first accomplished, today we can gratefully acknowledge practically complete replacement therapy with restoration to useful activity for

the victims of this formerly fatal disease. The task in medicine of recognizing a disease entity, understanding its pathology and pathological physiology and perfecting its treatment has been realized to a large extent. It is all the more gratifying that Thomas Addison's discovery and the endeavors it stimulated have disclosed so much of importance to the understanding of human physiology and have led to the development of the cortisones, and through them to the amelioration of much human suffering.

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*DISCUSSION*

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The first paragraph of Dr. Sorkin's paper depicts an argument between a Dr. George Harley and Thomas Addison concerning the validity of Addison's hypothesis that the adrenal glands are essential for life. The argument was apparently vigorous and Addison made it personal when he said, "In this case I foretold," and then asked the question, "Will Dr. Harley tell me, etc." This incident set the pattern which was to continue for the next 100 years.

Recognition of the concept of internal secretions and actual isolation of the first hormone, epinephrine, in 1901 only added fuel to the fire. The members of the American Society of Physiologists were entertained for several successive years at their annual meetings by the bitter controversy between W. B. Cannon and G. N. Stewart.

In 1924 G. N. Stewart expressed himself in more tolerant vein, as follows: "It must be remembered, however, that when nothing was known of the function of the thyroid or of the internal secretion of the pancreas a favorite assumption was that the serious consequences of their removal were due to the loss of a 'detoxicating' action, in the absence of which toxic substances which could no longer be neutralized, accumulated in the body. As soon as it was established that thyroid 'substitution therapy' was a brilliant success, especially when the specific hormone of the thyroid was isolated, nobody talked any more of the detoxicating function of the gland. It is the same now with the pancreas. It was the same for a time with the adrenals after the discovery of epinephrine. When it was seen, after the first enthusiasm had passed, that the discovery of epinephrine had not in any important degree solved the riddle of adrenal function, the ghost of the 'detoxication' theory began to walk again."

Six years later the first substantial confirmation of Addison's hypothesis was made. Substitution therapy was achieved with the extract of the adrenal cortex. This announcement was of first importance but for a time it was clouded by stinging words and personal attacks between the various research workers. They and their friends carried on the

pattern of controversy which started in 1855.

The outstanding contribution of Loeb that an adequate amount of sodium chloride in the diet improved the clinical condition of patients who had Addison's disease was followed by the observation that the toxic symptoms associated with nausea and weakness were related to a high intake of potassium. The obvious remedy was to restrict the intake of potassium in the diet. This lowered the concentration of potassium in the blood and benefited the patient. But this regimen was a two-edged sword. The patient became hypersensitive to a sudden large intake of potassium and the innocent ingestion of food with high content of potassium could prove fatal. This precarious situation was relieved, dramatically, in 1937 by Steiger and Reichstein by the first preparation of a hormone of the adrenal cortex, desoxycorticosterone. The compound influenced the retention of sodium and the excretion of potassium.

To some it seemed possible that, at last, the function of the adrenal gland was known and that all arguments were settled. But this interval did not last long. Britton and his associates continued to insist that the prepotent function of the adrenal gland was concerned, not with mineral metabolism, but with carbohydrate metabolism. And now harsh comment and caustic utterances arose over this question.

Britton carried out experiments which gave substance to his argument. Furthermore, it was observed that some patients treated with desoxycorticosterone died, even though their mineral metabolism was normal. More research was needed but the supply of the hormones which influenced carbohydrate metabolism was limited. At that time the most promising hormones which affected organic metabolism were known as compounds E and F.

The National Research Council decided to encourage and promote research concerned with preparation of these hormones. Hush-hush information which came by way of the grapevine was helpful. At a conference held at Yale University in the summer of 1941 a statement was made that Germany was buying large quantities of adrenal glands from Argentina and that the pilots of the Luftwaffe were supermen because they were sustained by an extract of the adrenal gland. This rumor, subsequently discredited, served as a powerful stimulant.

In October 1941 the first of a series of conferences of the National Research Council was held in Washington, D. C. All laboratories that could work on the problem were urged to send representatives. A strong

attack on the synthesis of compound E was made during 1942, 1943, 1944.

When the United States entered the second World War, December, 1941, three items were at the top of the agenda of the OSRD of the National Research Council. These were penicillin, anti-malarial compounds and hormones of the adrenal cortex. The first two yielded to research but compound E was not made available until much later.

A method for the preparation of compound A was devised in my laboratory in 1944 and a large sample was prepared by Merck and Co. in 1945. This was given to experimental animals and patients in the spring of 1946. The results were discouraging. The material was of no value. March 1946 was a low point.

There were plenty of critics who took the place of Dr. George Harley and for a time continued research was jeopardized. The project to make compound E available was carried on but everyone realized that this was the last chance. If compound E was not more active than compound A chemical investigation of the adrenal cortex would be terminated.

Two years of continuous effort passed before a method for preparation of compound E was at hand. Essential reactions were worked out in my laboratory and by Dr. L. H. Sarett at Merck and Co. A meeting of clinicians and physiologists was called on April 29, 1948. This meeting marked the lowest point of the project for no one could suggest a really important use for the hormone. One member said that he would not be interested until compound E was prepared in a form soluble in water.

During the summer of 1948 small samples of compound E were sent to several research institutions. There they remained untested. No one could foresee that within less than a year compound E would be known as cortisone and would be worth $200.00 a gram.

In August 1948 a few grams of compound E became available in my laboratory. It was first used to treat a patient who had Addison's disease. The response was prompt and striking. Dr. Hench and I then decided to carry out an experiment which we had discussed and planned seven years before. In 1941 after a conference in my laboratory Dr. Hench wrote in his note book, "Try compound E in rheumatoid arthritis."

I shall not add anything to what Dr. Sorkin has written about this phase of the investigation of the hormones of the adrenal cortex, but I would like to mention one incident. In the fall of 1954 rumors rapidly

spread about two new compounds which were much more effective than cortisone or hydrocortisone for the treatment of rheumatoid arthritis. No one knew exactly the chemical structures of the compounds but they were designated as metacortandralone and metacortandracine. In January 1955 I attended a dinner at the Waldorf Astoria and had the good fortune to sit next to a friend of mine who also was an official of the company which made the two new products. During the dinner I asked my neighbor when the identity of the two compounds would be made public. He said, "Next week and when you know what they are, you will be the most surprised man." I was surprised and so was everyone else. The new compounds were not revolutionary in nature. They were cortisone and hydrocortisone with a second double bond in the A ring.

Later in 1955 another company prepared methyl derivatives of cortisone and hydrocortisone. Still another company made halogen derivatives of the hormones. One wonders how long this type of research will continue. On this point Dr. Sorkin was cautious. He said, "knowledge of the chemical nature of the adrenocortical hormones probably has been completed." I believe the word "probably" should be left in place.

I shall now return to Thomas Addison. It is superfluous for me to say that Addison's place in medical history is secure. It has been several decades since anyone has criticized his statement that the adrenal glands are essential for life. Moreover the ghost of the intoxication theory walks no more through research laboratories.

Through use of classical methods the chemist has separated, identified and made available essential hormones of the adrenal cortex. By 1950 the clock had gone almost full circle. The time had arrived when the most audacious experiment could be tried—complete adrenalectomy in the human being—intentionally induced Addison's disease.

The procedure which once would have been wanton and criminal homicide was carried out by C. B. Huggins as a treatment for certain forms of carcinoma. The first four patients died but today several hundred human beings, perhaps as many as two thousand, have survived complete adrenalectomy and are maintained by substitution therapy with the hormones of the adrenal cortex. They are a living testimony to Thomas Addison, the pioneer in clinical research, who had the ability to observe, the genius to create and the courage to publish his conclusions.

## *DISCUSSION*

ABBIE INGALLS KNOWLTON

Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University, Assistant Attending Physician, Presbyterian Hospital, New York

I would like to say how much I have enjoyed hearing Dr. Sorkin's paper this evening. His excellent review has provided us with a very impressive panorama of how our current knowledge of adrenal physiology developed historically—beginning with Addison's fundamental contribution which established the link between the adrenal and the disease which now bears his name, through the confusing period when the separate nature of the cortical and the medullary secretions was not clearly defined, to the recognition of the role played by the cortex in regulating sodium metabolism and finally, to the present era in which the isolation and synthesis of the individual adrenal cortical steroids have permitted intensive study of their physiological actions.

In addition, it has been a privilege to hear Dr. Kendall's discussion, for his brilliant investigations have furnished most exciting chapters in the recent history of adrenal physiology.

This survey forms an impressive history and one which inevitably leads to speculation as to what the next chapters in the story will be. A variety of new techniques has been developed within the last few years—methods for the isolation and positive identification of steroids in the blood, for perfusing adrenal glands *in vitro*, for tissue culture and tissue slice study employing radioactive tracers. In addition, new variants of the known steroids have been synthesized. The application of each of these new investigative tools has already provided some material for future chapters. What will these chapters contain?

Most eagerly we await information as to the action of the adrenal hormones at a cellular level. Although we know much concerning the over-all effects of these hormones in the intact animal, as yet we know virtually nothing about the actual chemical changes in cellular metabolism by which the steroids exert their effects.

Three other chapters promise to be of particular interest: the first being that describing the more precise definition of the nature of the adrenal secretion; that is, what steroids comprise it and what constitute the stimuli to its secretion. Already it seems clear that only a few of the

steroids found in adrenal tissue occur in physiologically important amounts in the adrenal vein blood. In man these would seem to be Dr. Kendall's Compound F and Compound B, as well as aldosterone. It is known that the total amount of hormone secreted in the course of a day can vary over ten-fold, but little is known as yet about variations in the proportions of the individual component steroids in response to different stimuli. It *is* known that the increased hormone secretion which is evoked by ACTH is chiefly composed of hydrocortisone and corticosterone, the aldosterone output being increased but little or not at all; and the augmented excretion of aldosterone which follows upon sodium restriction can occur even in situations in which the secretion of hydrocortisone is much suppressed. These two observations suggest that the output of these two groups of steroids into the adrenal vein blood may vary independently, although the consistency with which both groups are deficient in the patient with Addison's disease implies the existence of some interrelationship. If ACTH is not the primary stimulus to aldosterone secretion, what is? Currently there are two schools of thought: one considers that the output of aldosterone varies with the potassium content of the diet, the other believes that the state of hydration is the primary factor influencing its secretion. Undoubtedly future studies will clarify these questions.

A second chapter, material for which is already being accumulated, will describe the pathways involved in steroidogenesis, the enzyme systems which operate and the level at which ACTH exhibits its stimulatory action. Already such studies have found clinical application: the adrenogenital syndrome is recognized at present as the expression of specific abnormalities in steroid elaboration. The correlation here between the clinical picture and the chemical nature of the secreted hormones has raised our understanding of this condition from the level of the curiosity of a side show visitor to one of intellectual insight which has made possible a rational therapeutic approach.

Thirdly, it seems to me that the cyclopenanthrene nucleus is currently the steroid chemist's Christmas tree. He can hang a halogen radical at a certain point or introduce a double bond at another, and the resulting changes in the metabolic activity of the compound may be startling. The future chapter incorporating the history of these synthetic modifications may well increase our understanding of the fundamental relationships between the structure of a steroid and its function.

Finally, there is no question but that this Centenary finds the patient with Addison's disease in a happy position indeed, as Dr. Sorkin and Dr. Kendall have said. In contrast to the inevitable downhill course which Addison pictured, today's patient can look forward to leading a close to normal life. The sodium abnormality can be easily corrected with supplements of sodium chloride and, when needed, a steroid to facilitate sodium retention. The oral effectiveness of fluorohydrocortisone makes the administration of such a steroid currently a simple matter. His appetite and general strength can be kept normal with small doses of cortisone or hydrocortisone. In the event of intercurrent illness or emergency operations, larger doses of hydrocortisone and attention to the maintenance of sodium balance will permit the patient to respond to these untoward happenings in much the manner that a normal would. We could wish that Addison could have been permitted to look ahead, as we have had the opportunity to look back this evening, and thereby fully appreciate the importance of his contribution made these one hundred years ago.

**MONTHLY PANEL MEETINGS ON THERAPEUTICS FOR THE GENERAL PHYSICIAN**

*Fifth Series — 1956-1957*

**Fridays at the Academy — 4:30 P.M.**

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*Moderator:* JOSEPH W. JAILER

*Members:* HENRY ARANOW, JR.
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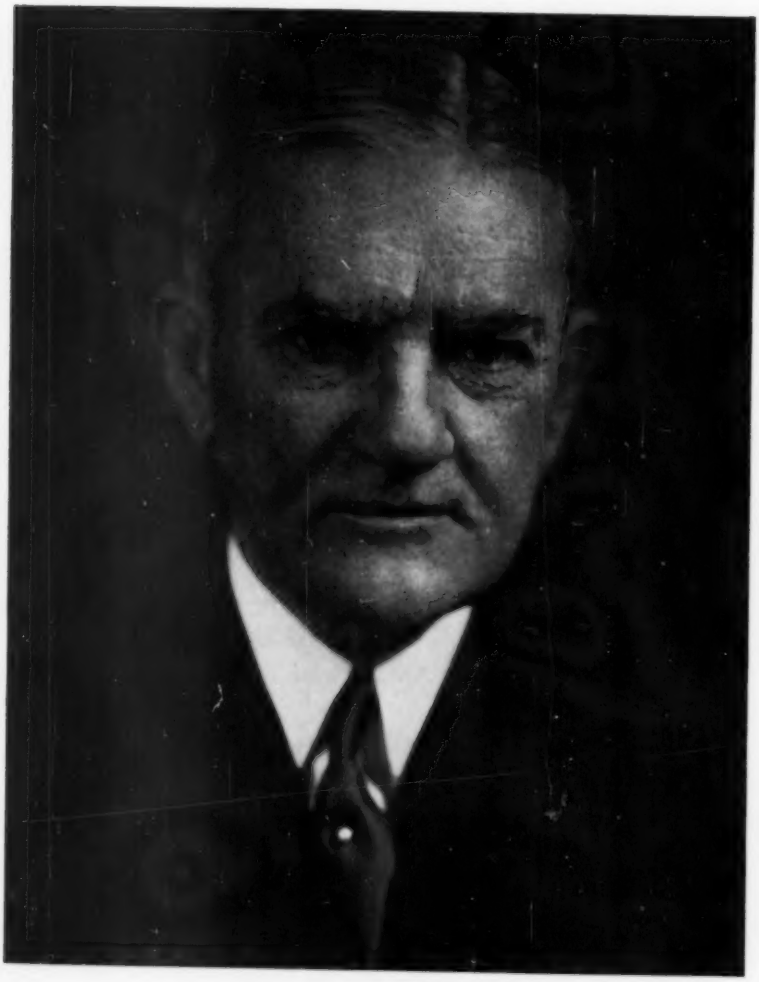

MALCOLM GOODRIDGE, M.D.

1873-1956

On July 16, 1956, there passed away one of the impressive figures in the history and the life of The New York Academy of Medicine. Malcolm Goodridge epitomized in his career the great physician, the lucid teacher and expositor and the dynamic public spirited citizen. Born in Flushing, N. Y., educated at Princeton and the College of Physicians and Surgeons, Columbia University, his early professional career was beset with illness which he overcame with the same courage and stamina which he later applied to the problems of the Academy. Deprived of an internship because of illness, he early became associated with St. Luke's Hospital and then with Bellevue Hospital where he displayed his unusual talents as a teacher of clinical medicine. Four decades of medical students and house officers look back on his teaching as an exciting and stimulating experience. New York Hospital, where he taught in his later years, honored him by electing him an Honorary Governor.

Dr. Goodridge's association with the Academy of Medicine began fifty years ago with his election to Fellowship in 1906. The list of his services is a long one. He was a member of the Committee on Public Health Relations for eleven years and was Vice-Chairman of the Committee on Activities. As President of the Academy for four years, he shouldered the heavy responsibilities of the pre-war and early war years of 1939 to 1942. He then served wisely and sagaciously as a Trustee during the financially perilous post-war years to 1947. The Academy made him an Honorary Fellow in 1949 and an Honorary Member of the Trustees and Council in 1952. For all these distinguished services he was awarded, on January fifth, 1956, the Academy Plaque.

However, Dr. Goodridge's crowning contribution to the life of the Academy was his Chairmanship for more than four years of the Committee on Medicine and the Changing Order. The balance and soundness of the Report of this Committee, as well as its breadth and depth, was due in greatest part to the tact, the discernment, vision and wisdom of Malcolm Goodridge. It stands as a monument to the man who engineered it through times of sharp disagreement, past the pitfalls of minutiae and chauvinistic attitudes.

To those who carry on the torch he so valiantly bore, the life and career of Malcolm Goodridge stand as a shining example of courage, integrity and devotion to an institution which he knew represented the best in medicine. He will be sorely missed.

HOWARD REID CRAIG

# SECTION ON MICROBIOLOGY*

## ABSTRACTS OF PAPERS

Presented at the Meeting, December 21, 1955 at The New York Academy of Medicine

## *The Relation of a Circulating Endogenous Pyrogen to the Cause of Experimental Fever*

ELISHA ATKINS

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Despite extensive studies on the physiology of temperature regulation the stimuli which act upon the hypothalamus to cause the fevers of disease remain unknown. The recent recovery of a pyrogenic substance from leukocytes by Bennett and Beeson has added support to the hypothesis that fever may be due to cellular injury in diseases involving inflammation. However, no such substance has hitherto been detected in the circulation.

The present studies deal with the presence of an endogenous pyrogen in the blood stream of rabbits made febrile by the injection of typhoid vaccine. Three types of donor animals were employed: 1) unsensitized donors, not previously challenged with vaccine; 2) "sensitized" donors which had received several previous injections spaced at intervals to obviate the development of tolerance; and 3) donors made pyrogen-tolerant by daily injections of vaccine for a period of a week or more.

The donors were given a standard inoculation of vaccine. Their sera were then tested for pyrogenic activity in both normal and pyrogen-tolerant recipients. With this method of passive transfer the amount of circulating pyrogen in the donor animals could be measured at various intervals after inoculation. By comparison of the responses of the normal and tolerant recipients to each sample of serum it was further possible to differentiate the pyrogen present into exogenous (injected) and endogenous types. Endogenous pyrogen, like the leukocytic pyrogen described by Bennett and Beeson, was found to be as active in tolerant as in normal recipients. On the other hand, the pyrogenic effect of the uncleared vaccine, present in donor serum obtained shortly after injection, was almost completely inhibited in the tolerant recipients.

Characteristic patterns of pyrogenic activity were found in the sera of the three classes of donors following inoculation of the vaccine. In sensitized donors, the clearance of the injected pyrogen was complete before the appearance of the endogenous form. In unsensitized donors, on the other hand, the endogenous pyrogen appeared before their circulations were cleared of the vaccine, resulting in a persistent level of pyrogenic activity throughout. Finally, in tolerant donors, no transferable pyrogen was found at any of the tested intervals. The lack of detectable endogenous pyrogen in this latter group parallels the marked reduction in the febrile response of tolerant animals and has been attributed to the very

* Maclyn McCarty, *Chairman;* A. M. Pappenheimer, Jr., *Secretary.*

rapid clearance of injected vaccine by cells of the reticulo-endothelial system. Because of this, cellular damage, presumably the source of endogenous pyrogen, is believed to be minimized. In conformity with this concept is the finding that endogenous pyrogen reappeared in the sera of tolerant donors given an injection of vaccine after R-E blockade had been established with Thorotrast. In this regard Beeson has shown that the febrile response of tolerant donors to injected pyrogens is restored after Thorotrast. The association of detectable levels of endogenous pyrogen with the augmented febrile response supports the hypothesis that fever is due to the presence of endogenous pyrogen in the circulation.

A close correlation of the duration of fever in both unsensitized and sensitized donors with the presence of endogenous pyrogen in their sera similarly suggests such a causal relationship.

In further preliminary studies, fevers have been induced in rabbits with intrapharyngeal inoculations of group A hemolytic streptococci and intravenous injections of the viruses of influenza A, PR8 strain, and Newcastle disease (NDV). Sera transferred from these donors at the height of their fever several hours later caused characteristic pyrogenic responses in normal and virus-tolerant recipients.

The presence of a circulating endogenous pyrogen in these different forms of experimental fever is indicative of a common pathogenetic mechanism. The similarity of the properties thus far obtained of endogenous and leukocytic pyrogen suggests that the former may be a product of cellular injury. In addition, the rapid onset of fever following the injection of the endogenous substance suggests that it may well be the factor which acts upon the hypothalamus to cause fever.

# *Studies of the Febrile Response to Acute Bacterial Infection and Bacterial Pyrogens**

IVAN L. BENNETT, JR.** and WILLIS R. KEENE***

Biological Division of the Department of Medicine, Johns Hopkins University, Baltimore, Maryland

Although some bacteria[1] and a few viruses[2] will provoke high fever when injected into man or experimental animals, many pathogenic microorganisms possess no demonstrable pyrogen, and fever, of course, accompanies many diseases that do not involve any known infectious agent. Because the obvious common denominator of disease is injury to cells, the hypothesis most commonly offered states that fever results from the action of products of tissue damage upon the cerebral centers governing body heat.[3] It is the purpose of this presentation to review briefly some of a series of experimental investigations that bear on this hypothesis.

At the outset, in the study of tissue substances which may produce fever, it is imperative to avoid contamination of test-materials with ordinary bacterial pyrogens. These substances are complex polysaccharides, the endotoxins or somatic antigens characteristic of gram-negative bacteria.[1, 4] They are active in small amounts and are able to withstand autoclaving for several hours without appreciable loss of potency. Because bacterial pyrogens are convenient agents for the production of experimental fever, their action has been studied extensively. Some of the facts which have been learned about the febrile response to injection of bacterial pyrogens are important to an understanding of the problem of studying products of tissue injury as possible factors in the pathogenesis of the fever of disease:

1. The injection of bacterial pyrogens directly into the blood stream of man or experimental animals is followed by a time lag or "latent" period before abrupt rise in body temperature occurs. In the rabbit, this delay amounts to 20-30 minutes; in man, it may be as long as 90 minutes. This lag-period is usually interpreted as indicating that bacterial pyrogens act *indirectly* to cause fever, that some preliminary reaction in the circulating blood or other tissues of the host is necessary to trigger the final stimulus to the central nervous system.[5, 6]

2. The febrile response of the rabbit to intravenous injection of bacterial pyrogen is typically biphasic with an initial rise and fall and a secondary spike.[7]

3. With daily injections of bacterial pyrogen, rabbits (or human subjects) develop a state of resistance to the fever-producing effect of these substances.[8] This "tolerance" is non-specific and is effective against pyrogens from any species of bacteria. It disappears rapidly when daily injections are stopped. The mechanism of pyrogen tolerance is incompletely understood but the observation by Beeson[8] that it is abolished by injection of particulate materials such as Thorotrast has led to the suggestion that it is a non-specific increase in the ability of cells of the so-called reticulo-endothelial system to remove pyrogen from the circulation and prevent its injurious effects. The recent observation of Braude[9] that the degree of tolerance is proportional to the speed with which labelled pyrogen is cleared from the blood stream supports this idea strongly. Humoral factors probably play some part in tolerance also.[7]

In the experiments to be described pyrogen contamination was avoided by sterilizing glassware, needles, etc., at 170°C. for two hours and by testing all solutions and reagents by injection into rabbits before use.

* The investigations that form the basis for this report have been supported by the U. S. Public Health Service, including Grant A-660 of the National Institute of Arthritis and Metabolic Diseases.

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If injured tissues release a substance or substances capable of producing fever, it might be supposed that normal tissues contain fever-promoting substances. Consequently a survey of normal tissues and cells of the rabbit for such a substance was carried out.[10] Normal tissues, including suspensions of macrophages and lymphocytes, were ground in various ways and saline extracts or suspensions were tested by intravenous, intramuscular, intraperitoneal and intrapleural injection into normal rabbits. Similarly, tissues were allowed to undergo sterile autolysis before preparation of extracts or suspensions for testing. Erythrocytes were damaged *in vitro* and reinjected and intravascular hemolysis was produced by injection of distilled water or saponin. Finally, rabbits were subjected to a series of operative procedures resulting in infarction of heart, lung, spleen, or kidney, their temperatures being followed carefully over 21 days postoperatively. None of the tissue preparations or other procedures resulted in fever in test animals.

Saline extracts of acute inflammatory lesions such as the Arthus reaction in rabbits were found to contain a fever-producing substance.[10] The febrile response of normal rabbits to injection of these extracts was monophasic and of brief (three to four hours) duration and the ability of extracts to produce fever was destroyed by heating at 90°C. for 30 minutes, evidence that bacterial contamination was not a factor.

It was finally shown that saline extracts of polymorphonuclear leukocytes collected from saline-induced peritoneal exudates in rabbits or from peripheral blood produced a similar monophasic febrile response as did the cell-free fluid of sterile peritoneal exudates.[11] However, saline injected into the peritoneal cavity of rabbits made neutropenic by nitrogen mustard resulted in the appearance of a fever-producing substance in peritoneal fluids containing no polymorphonuclear cells. The ability of these fluids and extracts to produce fever was destroyed by heating at 90°C. for 30 minutes.

The nature of this fever-producing substance is not yet clear. It is destroyed at 85°C. at pH 7.2 and at 70°C. at pH 4.5. It is non-dialyzable and its activity is uninfluenced by digestion with trypsin, chymotrypsin or ribonuclease. Daily injections produce no tolerance and the ability of rabbits to respond to it is uninfluenced by prior injection of Thorotrast. Present efforts are directed toward fractionating these materials by zone electrophoresis but results to date have not been definitive. The finding of this substance in sterile peritoneal fluids collected from neutropenic animals indicates that the polymorphonuclear leukocyte is not its only source; however, a recently completed survey of extracts of tissues of leukopenic animals again failed to reveal another origin.[12] A similar, perhaps the same, fever-promoting substance has been extracted regularly from the tissues of anaphylactically sensitized animals made febrile by reinjection of antigen.[13]

Peritoneal exudate and thoracic duct lymph collected from rabbits with Type I pneumococcal peritonitis also contain a heat-labile, fever-producing substance with properties similar to those already described.[14] This substance appears when animals develop fever several hours after inoculation of bacteria into the peritoneum and is no longer demonstrable after animals become afebrile as a result of treatment with penicillin. Its presence in thoracic duct lymph, of course, indicates its access to the venous circulation but extensive efforts to detect the fever-promoting factor in peripheral blood have thus far failed. The pneumococcus is not a pyrogen-producing organism. The course of events described in pneumococcal infections holds for both normal and nitrogen-mustard treated rabbits.[15] Failure to find a tissue pyrogen in the blood stream is probably due to technical difficulties in dosage; the injection of a large quantity of leukocyte extract into the circulating blood of normal rabbits is followed by its complete disappearance from the circulation within less than two minutes.[16] Further studies of these tissue pyrogens are in progress.

The mechanism of action of bacterial pyrogens has been subjected to study by several groups of investigators during the past few years. It has been shown by Grant and Whalen[17] and by Atkins and Wood[18] that the febrile response to intravenously injected

bacterial pyrogen is accompanied by the appearance in the circulation of a fever-producing substance that differs from the original pyrogen in several important respects, including the fact that it will produce fever after a much-shortened latent period. Furthermore, Atkins and Wood[19] have demonstrated that this material is fully as active in producing fever in tolerant as in normal animals, that it does not appear in the blood of tolerant rabbits unless they have been given Thorotrast, and that the febrile response to this "endogenous pyrogen" is monophasic and of brief duration, resembling the fever produced by leukocyte extracts. Atkins and Wood point out the regular occurrence of severe neutropenia immediately after injection of bacterial pyrogen and suggest that injury to leukocytes and probably other cells with release of tissue pyrogens is the "preliminary step" during the latent period before fever begins. Other evidence supports the idea that endotoxins injure leukocytes.[20] Rabbits made neutropenic with nitrogen mustard are capable of responding to bacterial pyrogens with fevers as high as those of normal animals[21] although Stetson and Good[22] have shown clearly that the leukopenic response to endotoxins is an essential part of the mechanism whereby these substances are able to elicit the Shwartzman reaction in rabbit skin.

The development in this laboratory of a simple technique for permanent implantation of polyethylene catheters into the subarachnoid space of the rabbit has made feasible the investigation of the possible direct effect of bacterial pyrogen upon the central nervous system. The evidence for direct action on nervous tissue of endotoxins has recently been summarized by Thomas.[4] It was reported by Tschirgi[23] that intrathecal injection of tiny amounts of pyrogen produced fever in the dog after a latent period of only five minutes. Observations made in rabbits given single or multiple injections of endotoxin intrathecally can be summarized briefly.

1. Injection of endotoxin into the basilar cistern or other portions of the subarachnoid space is followed by high fever. Injection of physiologic saline, normal serum, or erythrocytes is without effect on body temperature.

2. To produce comparable fever, more than 4000 times the amount of endotoxin is required by the intravenous as by the intrathecal route.

3. Sustained rise in rectal temperature often begins less than two minutes after intrathecal injection of pyrogen. If the latent period is arbitrarily defined as the time required for rectal temperature to rise 1°F., the latent period is invariably 12 to 16 minutes shorter for intrathecal injection than for the intravenous route.

4. Tolerance acquired by daily *intravenous* injections of pyrogen exerts no influence upon the febrile response to intrathecal pyrogen and daily *intrathecal* injections have thus far produced no tolerance.

5. The febrile response to intrathecal pyrogen is prevented by amidopyrine and by cortisone, in appropriate dosage.

6. There is no immediate leukopenia after injection of pyrogen into the cerebrospinal fluid and thus far, no "endogenous" pyrogen has been demonstrable in the blood of animals made febrile by injection of endotoxin by this route.

7. The febrile response of rabbits to intrathecal injection of pyrogen is prolonged, lasting seven to eight hours in many instances, but to date, fever curves have invariably been monophasic; no secondary rises have been observed (in contrast to the usual biphasic fever curve after intravenous administration).

Although these results are preliminary, when taken with the findings of Atkins and Wood,[18, 19] they may be used as a basis for certain speculations. Bacterial pyrogens may act both *directly* and *indirectly* to produce fever. Such a dual mechanism might account for the biphasic fever curve in the rabbit. More rapid removal of injected pyrogen in tolerant animals could prevent tissue injury and lessen the portion of the fever produced by "endogenous" pyrogen although the central nervous system remains able to respond to exogenous or endogenous pyrogens. This train of events would explain several puzzling observations, including the "biphasic" fever curve as well as the ability of leukopenic rabbits to respond to pyrogen with

high fevers. Farr, Clark, Proffitt and Campbell[7] have pointed out that the lessening of the febrile response as animals become tolerant to pyrogens is first evidenced by disappearance of the secondary rise while it is only later that decrease in the first portion of the fever curve occurs. Finally, tolerance to pyrogens is never complete; animals continue to respond with low but distinct fevers even if daily injections are continued for many weeks. This persistent minimal febrile response could be explained by assuming that although tolerant animals eliminate injected pyrogen from the circulation rapidly enough to prevent tissue damage (and the "endogenous" pyrogen of Atkins and Wood fails to appear), enough of the injected pyrogen reaches the brain to exert a direct action upon nervous tissue which retains its sensitivity to this stimulus despite repeated exposures. These last suggestions are speculations and are indulged in only at the invitation of the Chairman of the Section on Microbiology. It is hoped that investigations now in progress will clarify some of the points that have been raised.

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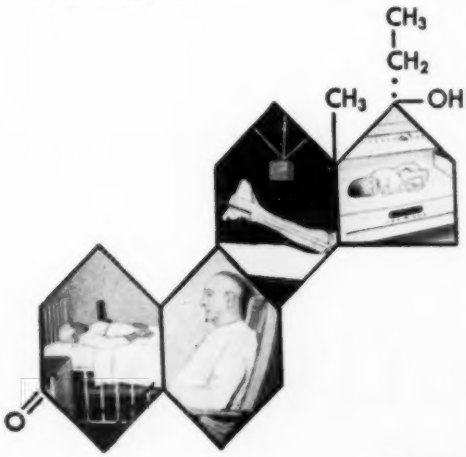


**OBJECTIVE AND SUBJECTIVE RESPONSE**—Orally effective, Nilevar therapy is characterized by retention of nitrogen, potassium, phosphorus and other electrolytes in ratios indicative of protein anabolism. Moreover, subjectively the patient observes an increase in appetite and sense of well-being.

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**SUPPLY**—Nilevar is available in uncoated, unscored tablets of 10 mg. G. D. Searle & Co., Research in the Service of Medicine.

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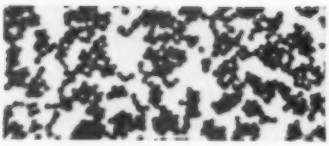

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## *Hospital Report Reveals Dannon Prune Whip Yogurt Successful in 95% of Chronic Cases When Taken Every Night for 3 Weeks*

*An important study of chronic constipation at a New York hospital discloses these striking results:**

In a group of 194 chronically ill patients, averaging 71.6 years of age, regular feeding of Dannon Prune Whip Yogurt produced excellent results. Completely normal bowel habits were re-established in 187 patients, or 95.8%. They required no laxatives during the period of administration. Improvement in skin tone, seborrheic dermatitis, intestinal stasis and pruritus ani were also noted.

Here is a natural, physiological approach which offers an effective solution to the widespread problem of faulty evacuation.

Dannon Prune Whip Yogurt is a smooth, custard-like milk food—highly palatable. Made from fresh milk, with about 50% of the butterfat removed, it is low in calories, high in nourishment and has the delicious flavor of old-fashioned prune whip. You may recommend Dannon Prune Whip Yogurt for your most stubborn constipation cases with the same gratifying results described in the above report. Prescribed regimen is to eat one container nightly before bedtime, for three weeks.

*Ferrer, F. P., and Boyd, L. J.: Am. J. Dig. Dis., 22:272, 1955

For literature, write Dannon Milk Products, Inc., 22-11 38th Avenue, Long Island City 1, N. Y.

*For dependable, prolonged increase in blood calcium levels...*

# In Hypocalcemic Tetany

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brand of dihydrotachysterol

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Since hypocalcemic tetany—usually the result of parathyroid deficiency—may require treatment for years, effective oral therapy with Hytakerol is superior to other methods.

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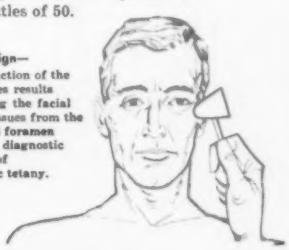
**"Dihydrotachysterol ... is of great therapeutic value in most cases of both normocalcemic and hypocalcemic tetany."**[2]

DOSAGE: Orally from 3 to 10 cc. (or from 6 to 20 capsules) daily until tetany is relieved; weekly maintenance dose from 1 to 7 cc. (or from 2 to 14 capsules) depending upon the blood and urine calcium levels. From 10 to 15 Gm. calcium lactate or gluconate should be given daily as supplement through the period of therapy.

SUPPLIED: Hytakerol in Oil, bottles of 15 cc.

Hytakerol Capsules (each equivalent to 0.5 cc.), bottles of 50.



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2. Sandock, Isadore: Tetany and ovarian function. *J.A.M.A.*, 160:659, Feb. 25, 1956.

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Tetracycline *Lederle*

*for prophylaxis and treatment of*

## obstetric infections

Posner and his colleagues[1] have reported on the use of tetracycline (ACHROMYCIN) in 96 cases of obstetric complications, including unsterile delivery, premature rupture of the membranes, endometritis, parametritis, and other conditions. They conclude that this antibiotic is ideally suited for these uses.

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ACHROMYCIN with STRESS FORMULA VITAMINS. Attacks the infection, bolsters the patient's natural defenses, thereby speeds recovery. Especially useful in severe or prolonged illness. Stress formula as suggested by the National Research Council.

SF Capsules, 250 mg.
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For more rapid and complete absorption. Offered only by Lederle!

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[1]Posner, A. C., *et al.*: Further Observations on the Use of Tetracycline Hydrochloride in Prophylaxis and Treatment of Obstetric Infections, *Antibiotics Annual* 1954-55, pp. 594-598.

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A recent Seminar at the New York Academy of Sciences emphasized the general acceptance by distinguished authorities of the hypothesis that psoriasis depends for its development upon a disturbance of fat metabolism.*

Clinical evidence indicates psoriasis may be due to a disturbance of the lipid metabolism, evidently caused by a deficiency of pancreatic enzymes.*

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*Each tablet contains:*
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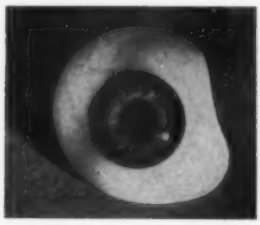

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**Reference:** 1. South M. J. 31:233, 1938.

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**REFERENCES:**
1. J.A.M.A. 159: 645 (Oct. 15) 1955.
2. J.A.M.A. 158: 386 (June 4) 1955.

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